Inventor Search

Harris 09/871,491

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=> d his

     (FILE 'MEDLINE' ENTERED AT 14:00:22 ON 15 NOV 2001)
               DEL HIS Y

     FILE 'MEDLINE, BIOSIS, WPIDS, HCAPLUS' ENTERED AT 14:03:30 ON 15 NOV 2001
               E RAULET D/AU
L1          305 S E3-4 OR E6-7
               E DIEFENBACH A/AU
L2           61 S E3 OR E6-7
L3          353 S L1 OR L2
L4          139 S NKG2D OR NKG2 D
L5           15 S L3 AND L4
L6            7 DUP REM L5 (8 DUPLICATES REMOVED)

=> d bib ab 1-7

L6   ANSWER 1 OF 7     MEDLINE
AN   2001468525     IN-PROCESS
DN   21404050   PubMed ID: 11513138
TI   Strategies for target cell recognition by natural killer cells.
AU   Diefenbach A; Raulet D H
CS   Department of Molecular & Cell Biology, University of California Berkeley,
     94720-3200, USA.
SO   IMMUNOLOGICAL REVIEWS, (2001 Jun) 181 170-84.
     Journal code: GG4; 7702118. ISSN: 0105-2896.
CY   Denmark
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   IN-PROCESS; NONINDEXED; Priority Journals
ED   Entered STN: 20010830
     Last Updated on STN: 20010830
AB   Stimulation of natural killer (NK) cells is regulated by a complex balance
     of inhibitory and stimulatory receptors expressed by NK cells. However,
     the interaction of stimulatory receptors and their ligands is poorly
     understood. One stimulatory receptor, NKG2D, is expressed by all
     NK cells, stimulated CD8+ T cells, gammadelta T cells and macrophages.
     Recently, progress has been made in defining cellular ligands for
     NKG2D. Four different families of ligands have been identified in
     mice and humans, all of which are distantly related to MHC class I
     molecules. Some of the ligands are upregulated in transformed and infected
     cells, provoking an attack by the innate and adaptive immune systems. It
     appears that these "induced-self" ligands recognized by the NKG2D
     receptor may be a precedent for a new strategy of target cell recognition
     by the immune system.

L6   ANSWER 2 OF 7     MEDLINE                                  DUPLICATE 1
AN   2001510266     MEDLINE
DN   21441910   PubMed ID: 11557981
TI   Rae1 and H60 ligands of the NKG2D receptor stimulate tumour
     immunity.
AU   Diefenbach A; Jensen E R; Jamieson A M; Raulet D H
CS   Department of Molecular and Cell Biology and Cancer Research Laboratory,
     University of California, Berkeley 94720, USA.
SO   NATURE, (2001 Sep 13) 413 (6852) 165-71.
     Journal code: NSC; 0410462. ISSN: 0028-0836.
CY   England: United Kingdom
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   200110
ED   Entered STN: 20010917
     Last Updated on STN: 20011022
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Entered Medline: 20011018

AB Natural killer (NK) cells attack many tumour cell lines, and are thought to have a critical role in anti-tumour immunity; however, the interaction between NK cells and tumour targets is poorly understood. The stimulatory lectin-like **NKG2D** receptor is expressed by NK cells, activated CD8+ T cells and by activated macrophages in mice. Several distinct cell-surface ligands that are related to class I major histocompatibility complex molecules have been identified, some of which are expressed at high levels by tumour cells but not by normal cells in adults. However, no direct evidence links the expression of these 'induced self' ligands with tumour cell rejection. Here we demonstrate that ectopic expression of the murine **NKG2D** ligands Rae1beta or H60 in several tumour cell lines results in potent rejection of the tumour cells by syngeneic mice. Rejection is mediated by NK cells and/or CD8+ T cells. The ligand-expressing tumour cells induce potent priming of cytotoxic T cells and sensitization of NK cells in vivo. Mice that are exposed to live or irradiated tumour cells expressing Rae1 or H60 are specifically immune to subsequent challenge with tumour cells that lack **NKG2D** ligands, suggesting application of the ligands in the design of tumour vaccines.

L6 ANSWER 3 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:210647 BIOSIS
DN PREV200100210647
TI The ligands for mouse **NKG2D** are expressed on tumor cells and activate NK cells and macrophages.
AU **Diefenbach, A. (1)**; Jamieson, A. M. (1); **Raulet, D. H. (1)**
CS (1) Department of Molecular and Cell Biology and Cancer Research Laboratory, University of California Berkeley, Berkeley, CA USA
SO Immunobiology, (November, 2000) Vol. 203, No. 1-2, pp. 436. print.
Meeting Info.: Joint Annual Meeting of the German and Dutch Societies of Immunology Duseldorf, Germany November 29-December 02, 2000
ISSN: 0171-2985.
DT Conference
LA English
SL English

L6 ANSWER 4 OF 7 MEDLINE DUPLICATE 2
AN 2001216034 MEDLINE
DN 21205390 PubMed ID: 11248803
TI Ligands for the murine **NKG2D** receptor: expression by tumor cells and activation of NK cells and macrophages.
CM Comment in: Nat Immunol. 2000 Aug;1(2):95-7
AU **Diefenbach A**; Jamieson A M; Liu S D; Shastri N; **Raulet D H**
CS Department of Molecular and Cell Biology and Cancer Research Laboratory, University of California, Berkeley, USA.
SO Nat Immunol, (2000 Aug) 1 (2) 119-26.
Journal code: DOG; 100941354. ISSN: 1529-2908.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200105
ED Entered STN: 20010521
Last Updated on STN: 20010521
Entered Medline: 20010517

AB Natural killer (NK) cells attack tumor and infected cells, but the receptors and ligands that stimulate them are poorly understood. Here we report the expression cloning of two murine ligands for the lectin-like receptor **NKG2D**. The two ligands, H-60 and Rae1 beta, are distant relatives of major histocompatibility complex class I molecules. **NKG2D** ligands are not expressed by most normal cells but are

up-regulated on numerous tumor cells. We show that mouse **NKG2D** is expressed by NK cells, activated CD8+ T cells and activated macrophages. Expression of either **NKG2D** ligand by target cells triggers NK cell cytotoxicity and interferon-gamma secretion by NK cells, as well as nitric oxide release and tumor necrosis factor alpha transcription by macrophages. Thus, through their interaction with **NKG2D**, H-60 and Rae1 beta are newly identified potent stimulators of innate immunity.

L6 ANSWER 5 OF 7 MEDLINE DUPLICATE 3
AN 2000045048 MEDLINE
DN 20045048 PubMed ID: 10574749
TI Natural killer cells: stress out, turn on, tune in.
AU **Diefenbach A; Raulet D H**
CS Department of Molecular and Cell Biology, Cancer Research Laboratory, 485 Life Sciences Addition, University of California at Berkeley, Berkeley, 94720-3200, USA.
SO CURRENT BIOLOGY, (1999 Nov 18) 9 (22) R851-3. Ref: 14
Journal code: B44; 9107782. ISSN: 0960-9822.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200005
ED Entered STN: 20000518
Last Updated on STN: 20000518
Entered Medline: 20000511
AB Natural killer cells attack tumor cells, infected cells and some normal cells, but the basis of their specificity is not completely understood. Recent studies indicate that epithelial tumor cells upregulate a stress-induced MHC class-I-like protein termed MICA, triggering NK cells via a recently described receptor called **NKG2D**.

L6 ANSWER 6 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:219315 BIOSIS
DN PREV199900219315
TI CD94 and NKG2 lectin-like receptors on mouse natural killer cells.
AU Vance, Russell E. (1); Kraft, Jennifer; Altman, John; Jensen, Peter; **Raulet, David H. (1)**
CS (1) University of California (Berkeley), Berkeley, CA USA
SO Natural Immunity, (Feb., 1998) Vol. 16, No. 2-3, pp. 91.
Meeting Info.: Fifth Annual Meeting of the Society for Natural Immunity Seventeenth International Natural Killer Cell Workshop Warrenton, Virginia, USA October 17-21, 1998
ISSN: 1018-8916.
DT Conference
LA English

L6 ANSWER 7 OF 7 MEDLINE DUPLICATE 4
AN 1998124458 MEDLINE
DN 98124458 PubMed ID: 9464811
TI Cloning of a mouse homolog of CD94 extends the family of C-type lectins on murine natural killer cells.
AU Vance R E; Tanamachi D M; Hanke T; **Raulet D H**
CS Department of Molecular and Cell Biology & Cancer Research Laboratory, University of California at Berkeley, 94720, USA.
NC RO1 AI35021 (NIAID)
SO EUROPEAN JOURNAL OF IMMUNOLOGY, (1997 Dec) 27 (12) 3236-41.
Journal code: EN5; 1273201. ISSN: 0014-2980.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS Priority Journals
OS GENBANK-AF030311; GENBANK-AF030312; GENBANK-AF030313
EM 199802
ED Entered STN: 19980306
Last Updated on STN: 19980306
Entered Medline: 19980220

AB Two families of major histocompatibility complex (MHC) class I-specific receptors are found on natural killer (NK) cells: immunoglobulin-like receptors and C-type lectin receptors. In mice, the latter category is represented by the Ly49 family of receptors, whereas in humans, NK cells express the distantly related CD94, which forms MHC class I-specific heterodimers with NKG2 family members. Humans also express the MHC class I-specific p50/p58/p70 family of immunoglobulin-like receptors, but these have not been identified in mice. Hence, there is no known instance of an MHC class I-specific receptor that is expressed by both human and murine NK cells. Here we report the cloning of CD94 from the CB.17 and C57BL/6 strains of mice. Mouse CD94 is 54% identical and 66% similar to human CD94, and is also a member of the C-type lectin superfamily. Mouse CD94 is expressed efficiently on the cell surface of cells transiently transfected with the corresponding cDNA, but surface CD94 was unable to mediate detectable binding to MHC class I-expressing ConA blasts. Notably, mouse CD94, like human CD94, has a very short cytoplasmic tail, suggesting the existence of partner chains that may play a role in ligand binding and signaling. Like many other C-type lectins expressed by NK cells, mouse CD94 maps to the NK complex on distal chromosome 6, synteneic to human CD94. We also demonstrate that mouse CD94 is highly expressed specifically by mouse NK cells, raising the possibility that mice, like humans, express multiple families of MHC class I-specific receptors on their NK cells. Murine homologs of human NKG2 family members have not yet been identified, but we report here the existence of a murine **NKG2D**-like sequence that also maps to the murine NK complex near CD94 and Ly49 family members.

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=> d his

     (FILE 'HOME' ENTERED AT 13:44:42 ON 15 NOV 2001)

     FILE 'HCAPLUS' ENTERED AT 13:44:46 ON 15 NOV 2001
L1            27 S NKG2D
L2             0 S NK G2D
L3            45 S NKG2D/AB
L4            81 S NKG2
L5             8 S L4 (2W) D
L6             8 S (NKG2 D)/AB
L7            57 S L1 OR L3 OR L5 OR L6
L8        360944 S TUMOR OR CARCINOMA? OR CANCER# OR NEOPLAS? OR MELENOMA?
L9        367140 S L8 OR MELANOMA?
L10            9 S L7 AND L8
L11            9 S L7 AND L9
L12       111394 S LIGAND#
L13            9 S L12 AND L7
L14            7 S L13 NOT L11

     FILE 'WPIDS' ENTERED AT 13:51:09 ON 15 NOV 2001
L15            1 S NKG2D OR NKG2 D

     FILE 'BIOSIS' ENTERED AT 13:51:37 ON 15 NOV 2001
L16           58 S NKG2D OR NKG2 D
L17      1015943 S TUMOR OR CARCINOMA? OR CANCER# OR NEOPLAS? OR MELANOMA?
L18           16 S L16 AND L17
L19           25 S LIGAND# AND L16
L20           15 S L19 NOT L18

     FILE 'HCAPLUS, BIOSIS' ENTERED AT 13:53:05 ON 15 NOV 2001
L21           21 DUP REM L11 L18 (4 DUPLICATES REMOVED)
L22           18 DUP REM L14 L20 (4 DUPLICATES REMOVED)
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=> d bib ab l21 1-21;d bib ab l22 1-18

L21 ANSWER 1 OF 21 HCAPLUS COPYRIGHT 2001 ACS
AN 2001:713586 HCAPLUS
DN 135:269070
TI Multifunctional proteins binding to **NKG2D** receptor complex and their use in treatment of **cancer**, infections, and autoimmune diseases
IN Kufer, Peter; Riethmueller, Gert; Lutterbuese, Ralf; Borschert, Katrin; Kischel, Roman; Mayer, Monika; Hofmeister, Robert
PA Germany
SO PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001071005	A2	20010927	WO 2001-EP3414	20010326

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI EP 2000-106467 A 20000324
AB The present invention relates to a multifunctional polypeptide comprising a first domain comprising a binding site specifically recognizing an extracellular epitope of the **NKG2D** receptor complex and a second domain having receptor or ligand function. Furthermore, the present invention relates to polynucleotides encoding the multifunctional polypeptide, to vectors comprising said polypeptides and to cells comprising said polynucleotides or said vectors. The invention also relates to compns. comprising either of the above recited mols., alone or in combination, as well as to specific medical uses of the multifunctional polypeptide of the invention. Thus, scFv proteins binding to **NKG2D** and Ep-CAM were produced. These scFv's recruited cytotoxic lymphocytes (CD8+ T cells and NK cells) and caused lysis of Ep-CAM-producing cells.

L21 ANSWER 2 OF 21 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:385890 BIOSIS
DN PREV200100385890
TI Receptors involved in human NK cell activation in the process of natural cytotoxicity.
AU Moretta, Lorenzo (1); Biassoni, Roberto; Bottino, Cristina; Mingari, Maria Cristina; Moretta, Alessandro
CS (1) Istituto Giannina Gaslini, 16148, Genova Italy
SO Cooper, Max D.; Takai, Toshiyuki; Ravetch, Jeffrey V.. (2001) pp. 199-209. Activating and inhibitory immunoglobulin-like receptors. print.
Publisher: Springer-Verlag Tokyo Inc. 3-13 Hongo 3-chome, Bunkyo-ku, Tokyo, 113-0033, Japan.
Meeting Info.: CREST International Symposium on Immunoglobulin-like Receptors Sendai City, Japan September 18-19, 2000
ISBN: 4-431-70297-0 (cloth).
DT Book; Conference
LA English
SL English

L21 ANSWER 3 OF 21 HCAPLUS COPYRIGHT 2001 ACS DUPLICATE 1
AN 2001:729002 HCAPLUS
TI Ectopic expression of retinoic acid early inducible-1 gene (RAE-1) permits natural killer cell-mediated rejection of a MHC class I-bearing **tumor** in vivo
AU Cerwenka, Adelheid; Baron, Jody L.; Lanier, Lewis L.
CS Department of Microbiology and Immunology and the Cancer Research Institute, University of California, San Francisco, CA, 94143-0414, USA
SO Proc. Natl. Acad. Sci. U. S. A. (2001), 98(20), 11521-11526
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
AB In 1986, Karre and colleagues reported that natural killer (NK) cells rejected an MHC class I-deficient tumor cell line (RMA-S) but they did not reject the same cell line if it expressed MHC class I (RMA). Based on this observation, they proposed the concept that NK cells provide immune surveillance for "missing self," e.g., they eliminate cells that have lost class I MHC antigens. This seminal observation predicted the existence of inhibitory NK cell receptors for MHC class I. Here, we present evidence that NK cells are able to reject tumors expressing MHC class I if the tumor expresses a ligand for **NKG2D**. Mock-transfected RMA cells resulted in tumor formation. In contrast, when RMA cells were transfected with the retinoic acid early inducible gene-1 .gamma. or .delta. (RAE-1), ligands for the activating receptor **NKG2D**, the tumors were rejected. The tumor rejection was mediated by NK cells, and not by CD1-restricted NK1.1+ T cells. No T cell-mediated immunol. memory against the parental tumor was generated in the animals that had rejected the RAE-1 transfected tumors, which succumbed to rechallenge with the parental RMA tumor. Therefore, NK cells are able to reject a tumor expressing RAE-1 mols., despite expression of self MHC class I on the tumor, demonstrating the potential for NK cells to participate in immunity against class I-bearing malignancies.
RE.CNT 33
RE
(1) Bahram, S; Adv Immunol 2000, V76, P1 HCAPLUS
(2) Bakker, A; Hum Immunol 2000, V61, P18 HCAPLUS
(3) Bauer, S; Science 1999, V285, P727 HCAPLUS
(4) Biron, C; Annu Rev Immunol 1999, V17, P189 HCAPLUS
(5) Bix, M; Nature (London) 1991, V349, P329 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 4 OF 21 HCAPLUS COPYRIGHT 2001 ACS DUPLICATE 2
AN 2001:298002 HCAPLUS
DN 135:60134
TI Role of **NKG2D** in **tumor** cell lysis mediated by human NK cells: cooperation with natural cytotoxicity receptors and capability of recognizing tumors of nonepithelial origin
AU Pende, Daniela; Cantoni, Claudia; Rivera, Paola; Vitale, Massimo; Castriconi, Roberta; Marcenaro, Stefania; Nanni, Marina; Biassoni, Roberto; Bottino, Cristina; Moretta, Alessandro; Moretta, Lorenzo
CS Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy
SO Eur. J. Immunol. (2001), 31(4), 1076-1086
CODEN: EJIMAF; ISSN: 0014-2980
PB Wiley-VCH Verlag GmbH
DT Journal
LA English
AB **NKG2D** is a recently described activating receptor expressed by both NK cells and CTL. In this study we investigated the role of **NKG2D** in the natural cytolysis mediated by NK cell clones. The role of **NKG2D** varied depending on the type of target cells analyzed. Lysis of various tumors appeared to be exclusively natural cytotoxicity receptors (NCR) dependent. In contrast, killing of another

group of target cells, including not only the epithelial cell lines HELA and IGROV-1, but also the FO-1 melanoma, the JA3 leukemia, the Daudi Burkitt lymphoma and even normal PHA-induced lymphoblasts, involved both NCR and **NKG2D**. Notably, NK cell clones expressing low surface densities of NCR(NCRdull) could lyse these tumors in an exclusively **NKG2D**-dependent fashion. Remarkably, not all of these targets expressed MICA/B, thus implying the existence of addnl. ligands recognized by **NKG2D**, possibly represented by GPI-linked mols. Finally, we show that the engagement of different HLA class I-specific inhibitory receptors by either specific antibodies or the appropriate HLA class I ligand led to inhibition of **NKG2D**-mediated NK cell triggering.

RE.CNT 37
RE
(1) Bauer, S; Science 1999, V285, P727 HCAPLUS
(2) Borrego, F; J Exp Med 1998, V187, P813 HCAPLUS
(3) Braud, V; Nature 1998, V391, P795 HCAPLUS
(4) Cantoni, C; Eur J Immunol 1998, V28, P327 HCAPLUS
(5) Cantoni, C; J Exp Med 1999, V189, P787 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 5 OF 21 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:267825 BIOSIS
DN PREV200100267825
TI Expression of **NKG2D** and MDL-1 on porcine myeloid cells.
AU Yim, Daesong (1); Jie, Hyun-Bae (1); Sotiriadis, John (1); Kim, Yoon-Sang (1); Shin, Soon Cheon (1); Lanier, Lewis L.; Kim, Yoon B. (1)
CS (1) Finch University of Health Sciences/The Chicago Medical School, 3333 Green Bay Road, North Chicago, IL, 60064 USA
SO FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A692. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DT Conference
LA English
SL English
AB **NKG2D** is a C-type lectin family receptor that associates with DAP10, recognizing **tumor** antigens such as MICA/B, RAE-1 and H60. We cloned porcine **NKG2D** receptor cDNA by RT-PCR. Porcine **NKG2D** cDNA has an open reading frame of 642 bp. Its expected polypeptide sequence is 214 amino acids. Porcine **NKG2D** has 66% sequence identity with human **NKG2D** and 56% identity with mouse **NKG2D**. RT-RCR analysis reveals that porcine **NKG2D** transcripts are expressed in PBL, NK cells, macrophages, and monocytes, but not in granulocytes. LPS upregulated **NKG2D** mRNA expression in macrophages. Porcine **NKG2D** gene is located on chromosome 5q25. When transiently transfected into COS-7 cells, porcine **NKG2D** requires DAP10 for cell surface expression. Myeloid DAP12-associating lectin-1 (MDL-1) is a type II membrane protein that associates with DAP12. Two isoforms of porcine MDL-1 cDNA were cloned from pulmonary alveolar macrophages. Porcine MDL-1 short form has 165 amino acids and 70% sequence identity with mouse MDL-1 short form. The long form has 20 more amino acids in the stalk region and 71% sequence identity with human MDL-1 and 67% with mouse MDL-1 long form. Porcine MDL-1 contains a conserved lysine in the transmembrane domain. MDL-1 transcripts were detected exclusively in macrophages and monocytes by RT-PCR. When transfected into 293 cells, porcine MDL-1 is expressed on the cell surface associated with DAP12. MDL-1 mRNA was detected in PBMC of neonatal "germ-free" piglets. Thus, MDL-1 may be involved in innate immunity.

L21 ANSWER 6 OF 21 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:275629 BIOSIS
DN PREV200100275629

TI **NKG2D**/DAP10: An immune receptor for oncofetal antigens.
AU Cerwenka, Adelheid (1); Lanier, Lewis L. (1)
CS (1) UCSF, San Francisco, CA, 94143 USA
SO FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A660. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DT Conference
LA English
SL English
AB NK cells are important effector cells in innate immunity providing protection against certain viral infections and tumors. A delicate balance between activating and inhibitory signals dictates their recognition of abnormal, distressed cells. We identified a family of cell surface proteins encoded by the retinoic acid inducible (RAE-1) genes and the H60 minor histocompatibility antigen that function as ligands for the mouse activating receptor **NKG2D**. Expression of these ligands is low in healthy adult tissue, but high in the embryo and on several **tumor** cell lines. Cell surface expression of RAE-1 molecules, which have low homology to classical MHC class 1 molecules, does not require the TAP transporter or beta2-microglobulin. Ectopic expression of RAE-1 in a MHC class 1 positive cell line confers target susceptibility to NK cell attack. Thus, the interaction between the receptor **NKG2D** expressed on NK cells with its ligands delivers a strong activating signal, which is able to overcome the self-MHC class 1 mediated inhibitory signals. These data emphasize the importance of the **NKG2D**-ligand interaction in NK cell activation and suggest a potential role in anti-**tumor** immunity.

L21 ANSWER 7 OF 21 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:536998 BIOSIS
DN PREV200100536998
TI Regulation of cutaneous malignancy by gammadelta T cells.
AU Girardi, Michael; Oppenheim, David E.; Steele, Carrie R.; Lewis, Julia M.; Glusac, Earl; Filler, Renata; Hobby, Paul; Sutton, Brian; Tigelaar, Robert E.; Hayday, Adrian C. (1)
CS (1) Peter Gorer Department of Immunobiology, Guy's King's St. Thomas' Medical School, King's College, London, SE1 9RT: adrian.hayday@kcl.ac.uk UK
SO Science (Washington D C), (19 October, 2001) Vol. 294, No. 5542, pp. 605-609. print.
ISSN: 0036-8075.
DT Article
LA English
SL English
AB The localization of gammadelta T cells within epithelia suggests that these cells may contribute to the down-regulation of epithelial malignancies. We report that mice lacking gammadelta cells are highly susceptible to multiple regimens of cutaneous carcinogenesis. After exposure to carcinogens, skin cells expressed Rae-1 and H60, major histocompatibility complex-related molecules structurally resembling human MICA. Each of these is a ligand for **NKG2d**, a receptor expressed by cytolytic T cells and natural killer (NK) cells. In vitro, skin-associated **NKG2d**+ gammadelta cells killed skin **carcinoma** cells by a mechanism that was sensitive to blocking **NKG2d** engagement. Thus, local T cells may use evolutionarily conserved proteins to negatively regulate malignancy.

L21 ANSWER 8 OF 21 HCAPLUS COPYRIGHT 2001 ACS
AN 2001:296377 HCAPLUS
DN 135:75404
TI Activating receptors and coreceptors involved in human natural killer

cell-mediated cytolysis
AU Moretta, Alessandro; Bottino, Cristina; Vitale, Massimo; Pende, Daniela; Cantoni, Claudia; Mingari, Maria Cristina; Biassoni, Roberto; Moretta, Lorenzo
CS Dip. Med. Sper., Universita degli Studi di Genova, Genoa, Italy
SO Annu. Rev. Immunol. (2001), 19, 197-223
CODEN: ARIMDU; ISSN: 0732-0582
PB Annual Reviews Inc.
DT Journal; General Review
LA English
AB A review and discussion with 127 refs. Natural killer cells can discriminate between normal cells and cells that do not express adequate amts. of major histocompatibility complex (MHC) class I mols. The discovery, both in mouse and in human, of MHC-specific inhibitory receptors clarified the mol. basis of this important NK cell function. However, the triggering receptors responsible for pos. NK cell stimulation remained elusive until recently. Some of these receptors have now been identified in humans, thus shedding some light on the mol. mechanisms involved in NK cell activation during the process of natural cytotoxicity. Three novel, NK-specific, triggering surface mols. (NKp46, NKp30, and NKp44) have been identified. They represent the first members of a novel emerging group of receptors collectively termed natural cytotoxicity receptors (NCR). A direct correlation exists between the surface d. of NCR and the ability of NK cells to kill various tumors. NKp46 is the only NCR involved in human NK-mediated killing of murine target cells. Accordingly, a homolog of NKp46 has been detected in mouse. Mol. cloning of NCR revealed novel members of the Ig superfamily displaying a low degree of similarity to each other and to known human mols. NCRs are coupled to different signal transducing adaptor proteins, including CD3.zeta., Fc.epsilon.RI.gamma., and KARAP/DAP12. Another triggering NK receptor is **NKG2D**. It appears to play either a complementary or a synergistic role with NCRs. Thus, the triggering of NK cells in the process of tumor cell lysis may often depend on the concerted action of NCR and **NKG2D**. In some instances, however, it may uniquely depend upon the activity of NCR or **NKG2D** only. Strict **NKG2D**-dependency can be appreciated using clones that, in spite of their NCRdull phenotype, efficiently lyse certain epithelial tumors or leukemic cell lines. Other triggering surface mols. including 2B4 and the novel NKp80 appear to function as coreceptors rather than as true receptors. Indeed, they can induce natural cytotoxicity only when co-engaged with a triggering receptor. While an altered expression or function of NCR or **NKG2D** is being explored as a possible cause of immunol. disorders, 2B4 dysfunction has already been assocd. with a severe form if immunodeficiency. Indeed, in patients with the X-linked lymphoproliferative disease, the inability to control Epstein-Barr virus infections may be consequent to a major dysfunction of 2B4 that exerts inhibitory instead of activating functions.
RE.CNT 111
RE
(1) Auchincloss, H; Annu Rev Immunol 1998, V16, P433 HCAPLUS
(2) Bakker, A; Immunity 2000, V13, P345 HCAPLUS
(3) Biassoni, R; Eur J Immunol 1997, V27, P3095 HCAPLUS
(4) Biassoni, R; Eur J Immunol 1999, V29, P1014 HCAPLUS
(5) Biassoni, R; J Exp Med 1996, V183, P645 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 9 OF 21 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:482112 BIOSIS
DN PREV200100482112
TI Rael and H60 ligands of the **NKG2D** receptor stimulate tumour immunity.
AU Diefenbach, Andreas; Jensen, Eric R.; Jamieson, Amanda M.; Raulet, David H. (1)

CS (1) Department of Molecular and Cell Biology and Cancer Research Laboratory, University of California, 485 Life Sciences Addition, Berkeley, CA, 94720: raulet@uclink4.berkeley.edu USA
SO Nature (London), (13 September, 2001) Vol. 413, No. 6852, pp. 165-171. print.
ISSN: 0028-0836.
DT Article
LA English
SL English
AB Natural killer (NK) cells attack many tumour cell lines, and are thought to have a critical role in anti-tumour immunity; however, the interaction between NK cells and tumour targets is poorly understood. The stimulatory lectin-like **NKG2D** receptor is expressed by NK cells, activated CD8+ T cells and by activated macrophages in mice. Several distinct cell-surface ligands that are related to class I major histocompatibility complex molecules have been identified, some of which are expressed at high levels by tumour cells but not by normal cells in adults. However, no direct evidence links the expression of these 'induced self' ligands with tumour cell rejection. Here we demonstrate that ectopic expression of the murine **NKG2D** ligands Raelbeta or H60 in several tumour cell lines results in potent rejection of the tumour cells by syngeneic mice. rejection is mediated by NK cells and/or CD8+ T cells. The ligand-expressing tumour cells induce potent priming of cytotoxic T cells and sensitization of NK cells in vivo. Mice that are exposed to live or irradiated tumour cells expressing Rael or H60 are specifically immune to subsequent challenge with tumour cells that lack **NKG2D** ligands, suggesting application of the ligands in the design of tumour vaccines.

L21 ANSWER 10 OF 21 HCAPLUS COPYRIGHT 2001 ACS DUPLICATE 3
AN 2001:229621 HCAPLUS
DN 135:18196
TI Recognition of **tumor** cells by the innate immune system
AU Soloski, Mark J.
CS Division of Rheumatology and the Program in Immunology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SO Curr. Opin. Immunol. (2001), 13(2), 154-162
CODEN: COPIEL; ISSN: 0952-7915
PB Elsevier Science Ltd.
DT Journal; General Review
LA English
AB A review with 88 refs. There has been a rapid increase in the authors' understanding of the cellular components of the innate immune system, the receptors used to distinguish changes in homeostasis, and how these components integrate into an anti-tumor effector response. Recently, significant progress has been made in the identification of ligands for receptors that activate NK cells, and the results have implications for the recognition of tumor cells.
RE.CNT 88
RE
(1) Aldrich, C; Cell 1994, V79, P649 HCAPLUS
(2) Amadou, C; Immunol Rev 1999, V167, P211 HCAPLUS
(3) Bakker, A; Immunity 2000, V13, P345 HCAPLUS
(4) Bakker, A; Proc Natl Acad Sci USA 1999, V96, P9792 HCAPLUS
(5) Bauer, S; Science 1999, V285, P727 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 11 OF 21 HCAPLUS COPYRIGHT 2001 ACS
AN 2001:297982 HCAPLUS
DN 135:59877
TI ULBPs, novel MHC class I-related molecules, bind to CMV glycoprotein UL16 and stimulate NK cytotoxicity through the **NKG2D** receptor
AU Cosman, David; Mullberg, Jurgen; Sutherland, Claire L.; Chin, Wilson;

Armitage, Richard; Fanslow, William; Kubin, Marek; Chalupny, N. Jan
CS Department of Molecular Biology, Immunex Corporation, Seattle, WA, 98101, USA
SO Immunity (2001), 14(2), 123-133
CODEN: IUNIEH; ISSN: 1074-7613
PB Cell Press
DT Journal
LA English
AB The human cytomegalovirus glycoprotein, UL16, binds to two members of a novel family of mols., the ULBPs, and to the MHC class I homolog, MICB. The ULBPs are GPI-linked glycoproteins belonging to the extended MHC class I family but are only distantly related to MICB. The ULBP and MICB mols. are ligands for the activating receptor, **NKG2D**/DAP10, and this interaction is blocked by a sol. form of UL16. The ULBPs stimulate cytokine and chemokine prodn. from NK cells, and expression of ULBPs in NK cell-resistant target cells confers susceptibility to NK cell cytotoxicity. Masking of NK cell recognition of ULBP or MIC antigens by UL16 provides a potential mechanism by which human cytomegalovirus-infected cells might evade attack by the immune system.
RE.CNT 45
RE
(1) Ando, H; Immunogenetics 1997, V46, P499 HCAPLUS
(2) Bahram, S; Proc Natl Acad Sci USA 1994, V91, P6259 HCAPLUS
(3) Bauer, S; Science 1999, V285, P727 HCAPLUS
(4) Baum, P; EMBO J 1994, V13, P3992 HCAPLUS
(5) Biron, C; Annu Rev Immunol 1999, V17, P189 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 12 OF 21 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:37271 BIOSIS
DN PREV200100037271
TI Soluble forms of the novel, MHC class 1-related molecules, ULBP1 and ULBP2, bind to, and functionally activate NK cells.
AU Chalupny, J. (1); Cosman, D. (1); Mullberg, J. (1); Chin, W. (1); Cassiano, L. (1); Means, G. (1); Derry, J. (1); Russell, C. (1); Armitage, R. (1); Sutherland, C. (1); Fanslow, W. (1); Kubin, M. (1)
CS (1) Immunex Corp, Seattle, WA, 98101 USA
SO FASEB Journal, (April 20, 2000) Vol. 14, No. 6, pp. A1018. print.
Meeting Info.: Joint Annual Meeting of the American Association of Immunologists and the Clinical Immunology Society Seattle, Washington, USA May 12-16, 2000
ISSN: 0892-6638.
DT Conference
LA English
SL English

L21 ANSWER 13 OF 21 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:552552 HCAPLUS
TI Exposing **tumor** cells to killer cell attack
AU Watzl, C.; Long, E. O.
CS Laboratory of Immunogenetics National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville, MD, 20852, USA
SO Nat. Med. (N. Y.) (2000), 6(8), 867-868
CODEN: NAMEFI; ISSN: 1078-8956
PB Nature America Inc.
DT Journal
LA English
AB Natural killer (NK) cells attack tumor and virally infected cells in the absence of antigen presentation, utilizing a combination of signals from activation and inhibitory receptors. Recent reports have identified the NK and T-cell surface protein **NKG2D** as a receptor for tumor cell ligands that activates killing of tumor targets.
RE.CNT 9

RE
(1) Bauer, S; Science 1999, V285, P727 HCAPLUS
(2) Cerwenka, A; Immunity 2000, V12, P721 HCAPLUS
(3) Chang, C; J Immunol 1999, V163, P4651 HCAPLUS
(4) Groh, V; Proc Natl Acad Sci 1999, V96, P6879 HCAPLUS
(5) Ljunggren, H; Immunol Today 1990, V11, P237 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 14 OF 21 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:210647 BIOSIS
DN PREV200100210647
TI The ligands for mouse **NKG2D** are expressed on **tumor** cells and activate NK cells and macrophages.
AU Diefenbach, A. (1); Jamieson, A. M. (1); Raulet, D. H. (1)
CS (1) Department of Molecular and Cell Biology and Cancer Research Laboratory, University of California Berkeley, Berkeley, CA USA
SO Immunobiology, (November, 2000) Vol. 203, No. 1-2, pp. 436. print.
Meeting Info.: Joint Annual Meeting of the German and Dutch Societies of Immunology Duseldorf, Germany November 29-December 02, 2000
ISSN: 0171-2985.
DT Conference
LA English
SL English

L21 ANSWER 15 OF 21 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:238053 BIOSIS
DN PREV200000238053
TI A single amino acid substitution causes loss of expression of a MICA allele.
AU Li, Zihai; Groh, Veronika; Strong, Roland K.; Spies, Thomas (1)
CS (1) Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., Seattle, WA, 98109 USA
SO Immunogenetics, (March, 2000) Vol. 51, No. 3, pp. 246-248.
ISSN: 0093-7711.
DT Article
LA English
SL English

L21 ANSWER 16 OF 21 HCAPLUS COPYRIGHT 2001 ACS DUPLICATE 4
AN 2000:557581 HCAPLUS
DN 133:236795
TI Ligands for the murine **NKG2D** receptor: expression by **tumor** cells and activation of NK cells and macrophages
AU Diefenbach, Andreas; Jamieson, Amanda M.; Liu, Scot D.; Shastri, Nilabh; Raulet, David H.
CS Department of Molecular and Cell Biology and Cancer Research Laboratory, University of California, Berkeley, CA, USA
SO Nat. Immunol. (2000), 1(2), 119-126
CODEN: NIAMCZ; ISSN: 1529-2908
PB Nature America Inc.
DT Journal
LA English
AB Natural killer (NK) cells attack tumor and infected cells, but the receptors and ligands that stimulate them are poorly understood. Here we report the expression cloning of two murine ligands for the lectin-like receptor **NKG2D**. The two ligands, H-60 and Rae-1.beta., are distant relatives of major histocompatibility complex class I mols. **NKG2D** ligands are not expressed by most normal cells but are up-regulated on numerous tumor cells. We show that mouse **NKG2D** is expressed by NK cells, activated CD8+T cells and activated macrophages. Expression of either **NKG2D** ligand by target cells triggers NK cell cytotoxicity and interferon-.gamma. secretion by NK cells, as well as nitric oxide release and tumor necrosis factor .alpha. transcription by

macrophages. Thus, through their interaction with **NKG2D**, H-60 and Rael.beta. are newly identified potent stimulators of innate immunity.

RE.CNT 41
RE
(1) Altman, J; Science 1996, V274, P94 HCAPLUS
(2) Amadou, C; Immunol Rev 1999, V167, P211 HCAPLUS
(3) Bahram, S; Proc Natl Acad Sci USA 1994, V91, P6259 HCAPLUS
(4) Bauer, S; Science 1999, V285, P727 HCAPLUS
(5) Brown, M; J Exp Med 1998, V188, P2083 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 17 OF 21 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:28283 BIOSIS
DN PREV200000028283
TI Natural killer cells: Stress out, turn on, tune in.
AU Diefenbach, Andreas (1); Raulet, David H. (1)
CS (1) Department of Molecular and Cell Biology and Cancer Research Laboratory, University of California at Berkeley, 485 Life Sciences Addition, Berkeley, CA, 94720-3200 USA
SO Current Biology, (Nov. 18, 1999) Vol. 9, No. 22, pp. R851-R853. ISSN: 0960-9822.
DT Article
LA English
SL English
AB Natural killer cells attack **tumor** cells, infected cells and some normal cells, but the basis of their specificity is not completely understood. Recent studies indicate that epithelial **tumor** cells upregulate a stress-induced MHC class-I-like protein termed MICA, triggering NK cells via a recently described receptor called **NKG2D**
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L21 ANSWER 18 OF 21 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:484525 BIOSIS
DN PREV199900484525
TI An activating immunoreceptor complex formed by **NKG2D** and DAP10.
AU Wu, Jun; Song, Yaoli; Bakker, Alexander B.H.; Bauer, Stefan; Spies, Thomas; Lanier, Lewis L. (1); Phillips, Joseph H.
CS (1) DNAX Research Institute, 901 California Avenue, Palo Alto, CA, 94304 USA
SO Science (Washington D C), (July 30, 1999) Vol. 285, No. 5428, pp. 730-732. ISSN: 0036-8075.
DT Article
LA English
SL English
AB Many immune receptors are composed of separate ligand-binding and signal-transducing subunits. In natural killer (NK) and T cells, DAP10 was identified as a cell surface adaptor protein in an activating receptor complex with **NKG2D**, a receptor for the stress-inducible and **tumor**-associated major histocompatibility complex molecule MICA. Within the DAP10 cytoplasmic domain, an Src homology 2 (SH2) domain-binding site was capable of recruiting the p85 subunit of the phosphatidylinositol 3-kinase (PI 3-kinase), providing for **NKG2D** -dependent signal transduction. Thus, **NKG2D**-DAP10 receptor complexes may activate NK and T cell responses against MICA-bearing tumors.

L21 ANSWER 19 OF 21 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:484524 BIOSIS
DN PREV199900484524
TI Activation of NK cells and T cells by **NKG2D**, a receptor for stress-inducible MICA.
AU Bauer, Stefan; Groh, Veronika; Wu, Jun; Steinle, Alexander; Phillips, Joseph H.; Lanier, Lewis L.; Spies, Thomas (1)

CS (1) Clinical Research Division, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, Seattle, WA, 98109 USA
SO Science (Washington D C), (July 30, 1999) Vol. 285, No. 5428, pp. 727-729. ISSN: 0036-8075.
DT Article
LA English
SL English
AB Stress-inducible MICA, a distant homolog of major histocompatibility complex (MHC) class I, functions as an antigen for gammadelta T cells and is frequently expressed in epithelial tumors. A receptor for MICA was detected on most gammadelta T cells, CD8+ alphabeta T cells, and natural killer (NK) cells and was identified as **NKG2D**. Effector cells from all these subsets could be stimulated by ligation of **NKG2D**. Engagement of **NKG2D** activated cytolytic responses of gammadelta T cells and NK cells against transfectants and epithelial **tumor** cells expressing MICA. These results define an activating immunoreceptor-MHC ligand interaction that may promote antitumor NK and T cell responses.

L21 ANSWER 20 OF 21 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:316201 BIOSIS
DN PREV199699038557
TI An autosomal dominant locus, Nka, mapping to the Ly-49 region of a rat natural killer (NK) gene complex, controls NK cell lysis of allogeneic lymphocytes.
AU Dissen, Erik (1); Ryan, James C.; Seaman, William E.; Fossum, Sigbjorn
CS (1) Dep. Anat., Inst. Basic Medical Sciences, Univ. Oslo, P.O. Box 1105, Blindern, N-0137 Oslo Norway
SO Journal of Experimental Medicine, (1996) Vol. 183, No. 5, pp. 2197-2207. ISSN: 0022-1007.
DT Article
LA English
AB Natural Killer (NK) cells can recognize and kill MHC-incompatible normal bone marrow-derived cells. Presently characterized MHC-binding receptors on NK cells, including the Ly-49 family in the mouse, transmit inhibitory signals upon binding to cognate class I MHC ligands. Here we study in vivo NK-mediated lysis of normal allogeneic lymphocytes in crosses between alloreactivity-competent PVG rats and alloreactivity-deficient DA rats. NK cells from both strains are able to lyse standard **tumor** targets. We identify an autosomal dominant locus, Nka, that controls NK-mediated alloreactivity. Individuals carrying the dominant PVG allele in single dose were fully competent in eliminating allogeneic target cells, suggesting that Nka encodes or regulates a gene product inducing or activating alloreactivity. By linkage analysis and pulsed field gel electrophoresis, a natural killer gene complex (NKC) on rat chromosome 4 is described that contains the rat NKR-P1 and Ly-49 multigene families plus a rat **NKG2D** homologue. Nka maps within the NKC, together with the most telomeric Ly-49 family members, but separate from **NKG2D** and the NKR-P1 family. The Nka-encoded response, moreover, correlates with the expression of transcripts for Ly-49 receptors in NK cell populations, as Northern blot analysis demonstrated low expression of Ly-49 genes in DA NK cells, in contrast to high expression in alloreactivity-competent PVG, (DA times PVG)F-1, and PVG.1AV1 NK cells. The low Ly-49 expression in DA is not induced by MHC haplotype, as demonstrated by high expression of Ly-49 in the DA MHC-congenic PVG.1AV1 strain. Finally, we have cloned and characterized the first four members of the rat Ly-49 gene family. Their cytoplasmic domains demonstrate substantial heterogeneity, consistent with the hypothesis that different Ly-49 family members may subserve different signaling functions.

L21 ANSWER 21 OF 21 HCAPLUS COPYRIGHT 2001 ACS
AN 1993:162459 HCAPLUS
DN 118:162459

TI NKG2 proteins of natural killer cells, cDNA encoding them, and methods for treatment of **cancer** or virus infection
IN Houchins, Jeffrey P.; Yabe, Toshio; McSherry, Cynthia M.; Bach, Fritz H.; Hofer, Erhard
PA University of Minnesota, USA; Sandoz Ltd.
SO PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9217198	A1	19921015	WO 1992-US2469	19920327
	W: JP, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE				
	EP 585257	A1	19940309	EP 1992-909331	19920327
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	JP 06506358	T2	19940721	JP 1992-508930	19920327
	US 6262244	B1	20010717	US 1995-543246	19951013
PRAI	US 1991-676663	A2	19910328		
	WO 1992-US2469	W	19920327		
	US 1993-122514	B1	19930924		

AB The cDNAs for 4 NKG2 proteins of human natural killer cells are cloned and sequenced. Antibodies to these proteins; chimeric antibodies recognizing NKG2 protein and a cancer- or virus-specific antigen; NKG2-cytotoxic protein fusion proteins; and the use of these antibodies or chimeric proteins for treatment of cancer or virus infection are claimed. The 4 cDNAs represent a new mammalian gene family. These proteins displayed significant sequence similarity only with type II transmembrane proteins with C-type animal lectin domains. The NKG2-C protein was manufd. with transgenic Sf9 cells and the extracellular domain of this protein manufd. as a fusion protein in Escherichia coli.

L22 ANSWER 1 OF 18 HCAPLUS COPYRIGHT 2001 ACS DUPLICATE 1
AN 2001:330267 HCAPLUS
DN 135:106137
TI Complex structure of the activating immunoreceptor **NKG2D** and its MHC class I-like **ligand** MICA
AU Li, Pingwei; Morris, Daniel L.; Willcox, Benjamin E.; Steinle, Alexander; Spies, Thomas; Strong, Roland K.
CS Division of Basic Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, 98109, USA
SO Nat. Immunol. (2001), 2(5), 443-451
CODEN: NIAMCZ; ISSN: 1529-2908
PB Nature America Inc.
DT Journal
LA English
AB The major histocompatibility complex (MHC) class I homolog, MICA, is a stress-inducible ligand for **NKG2D**, a C-type lectin-like activating immunoreceptor. The crystal structure of this ligand-receptor complex that the authors report here reveals an **NKG2D** homodimer bound to a MICA monomer in an interaction that is analogous to that seen in T cell receptor-MHC class I protein complexes. Similar surfaces on each **NKG2D** monomer interact with different surfaces on either the .alpha.1 or .alpha.2 domains of MICA. The binding interactions are large in area and highly complementary. The central section of the .alpha.2-domain helix, disordered in the structure of MICA alone, is ordered in the complex and forms part of the **NKG2D** interface. The extensive flexibility of the interdomain linker of MICA is shown by its altered conformation when crystd. alone or in complex with

NKG2D.
RE.CNT 53
RE
(1) Bahram, S; Immunogenetics 1996, V43, P230 HCAPLUS
(2) Bahram, S; Proc Natl Acad Sci 1994, V91, P6259 HCAPLUS
(4) Bauer, S; Science 1999, V285, P727 HCAPLUS
(5) Berman, H; Nucleic Acids Res 2000, V28, P235 HCAPLUS
(6) Boyington, J; Immunity 1999, V10, P75 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 2 OF 18 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:385993 BIOSIS
DN PREV200100385993
TI MICA and MICB genes: Can the enigma of their polymorphism be resolved.
AU Stephens, Henry A. F. (1)
CS (1) Institute of Urology and Nephrology, University College London, Middlesex Hospital, 48 Riding House Street, London, W1W 7EY: h.stephens@ucl.ac.uk UK
SO Trends in Immunology, (July, 2001) Vol. 22, No. 7, pp. 378-385. print. ISSN: 1471-4906.
DT General Review
LA English
SL English
AB The human MHC class I chain-related genes (MICA and MICB) are located within the HLA class I region of chromosome 6. Their organization, expression and products differ considerably from classical HLA class I genes. MIC proteins are considered to be markers of 'stress' in the epithelia, and act as **ligands** for cells expressing a common activatory natural killer-cell receptor (**NKG2D**). Molecular models are now available for the MICA protein, both bound and complexed with **NKG2D**. MICA molecules appear to be highly flexible and polymorphic, although the functional relevance and implications of their polymorphism have yet to be fully discerned.

L22 ANSWER 3 OF 18 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:291228 BIOSIS
DN PREV200100291228
TI Crystal structure of the complex between the stress-inducible MHC class I homolog MIC-A and the NK cell receptor **NKG2D**.
AU Strong, Roland K. (1); Li, Pingwei (1); Morris, Daniel L. (1); Steinle, Alexander (1); Spies, Thomas (1)
CS (1) Fred Hutchinson Cancer Research Center, Basic Sciences, 1100 Fairview Ave. North, Seattle, WA, 98109 USA
SO FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A321. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DT Conference
LA English
SL English
AB The major histocompatibility complex (MHC) class I homolog MIC-A functions as a stress-inducible antigen, expressed on intestinal epithelium and epithelially-derived tumors, that is broadly recognized by the Vdelta1-bearing subset of gammadelta T cells, CD8+ alphabeta T cells and NK cells independent of beta2-microglobulin and bound peptides. MIC-A recognition by these cells is mediated through interactions with the stimulatory NK receptor **NKG2D**, a divergent member of the C-type lectin-like family of proteins and a distant relative of other members of the NKG2 family of NK cell receptors and CD94. The crystal structure of the complex reveals that an **NKG2D** homodimer binds to a MIC-A monomer, contacting residues of both the alpha1 and alpha2 domains, in an interaction distinct from other NK receptor/**ligand** complex

structures. A section of the alpha2 domain helix, disordered in the structure of MIC-A crystallized on its own, is ordered in the complex and forms part of the MIC-A/**NKG2D** interface. Potential receptor binding sites on the underside of the platform, on the side opposite the surface recognized by alphabeta T cell receptors on MHC class I/peptide complexes, proposed on the basis of the MIC-A crystal structure, do not form part of the MIC-A/**NKG2D** interface in the crystal structure of the complex. Rather, these sites participate in extensive MIC-A/MIC-A crystal contacts yielding a MIC-A tetramer that recapitulates the interdomain relationship seen in conventional, beta2-microglobulin-binding MHC class I homologs.

L22 ANSWER 4 OF 18 HCAPLUS COPYRIGHT 2001 ACS DUPLICATE 2
AN 2001:481688 HCAPLUS
TI Interactions of human **NKG2D** with its **ligands** MICA, MICB, and homologs of the mouse RAE-1 protein family
AU Steinle, Alexander; Li, Pingwei; Morris, Daniel L.; Groh, Veronika; Lanier, Lewis L.; Strong, Roland K.; Spies, Thomas
CS Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, 98109, USA
SO Immunogenetics (2001), 53(4), 279-287
CODEN: IMNGBK; ISSN: 0093-7711
PB Springer-Verlag
DT Journal
LA English
AB **NKG2D** is an activating receptor that is expressed on most natural killer (NK) cells, CD8 .alpha..beta. T cells, and .gamma..delta. T cells. Among its ligands is the distant major histocompatibility complex class I homolog MICA, which has no function in antigen presentation but is induced by cellular stress. To extend previous functional evidence, the **NKG2D**-MICA interaction was studied in isolation. **NKG2D** homodimers formed stable complexes with monomeric MICA in soln., demonstrating that no other components were required to facilitate this interaction. MICA glycosylation was not essential but enhanced complex formation. Sol. **NKG2D** also bound to cell surface MICB, which has structural and functional properties similar to those of MICA. Moreover, **NKG2D** stably interacted with surface mols. encoded by three newly identified cDNA sequences (N2DL-1, -2, and -3), which are identical to the human ULBP proteins and may represent homologs of the mouse retinoic acid-early inducible family of **NKG2D** ligands. Because of the substantial sequence divergence among these mols., these results indicated promiscuous modes of receptor binding. Comparison of allelic variants of MICA revealed large differences in **NKG2D** binding that were assocd. with a single amino acid substitution at position 129 in the .alpha.2 domain. Varying affinities of MICA alleles for **NKG2D** may affect thresholds of NK-cell triggering and T-cell modulation.
RE.CNT 41
RE
(1) Bahram, S; Immunogenetics 1996, V43, P230 HCAPLUS
(2) Bahram, S; Proc Natl Acad Sci 1994, V91, P6259 HCAPLUS
(4) Bauer, S; Science 1999, V285, P727 HCAPLUS
(5) Bjorkman, P; Annu Rev Biochem 1990, V59, P253 HCAPLUS
(6) Bjorkman, P; Nature 1987, V329, P506 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 5 OF 18 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:410147 BIOSIS
DN PREV200100410147
TI Costimulation of CD8alphabeta T cells by **NKG2D** via engagement by MIC induced on virus-infected cells.
AU Groh, Veronika (1); Rhinehart, Rebecca; Randolph-Habecker, Julie; Topp, Max S.; Riddell, Stanley R.; Spies, Thomas (1)

CS (1) Clinical Research Division, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. North, Seattle, WA, 98109: vgroh@fred.fhcrc.org, tspies@fred.fhcrc.org USA
SO Nature Immunology, (March, 2001) Vol. 2, No. 3, pp. 255-260. print. ISSN: 1529-2908.
DT Article
LA English
SL English
AB **NKG2D** is an activating receptor that stimulates innate immune responses by natural killer cells upon engagement by MIC **ligands**, which are induced by cellular stress. Because **NKG2D** is also present on most CD8alphabeta T cells, it may modulate antigen-specific T cell responses, depending on whether MIC molecules-distant homologs of major histocompatibility complex (MHC) class I with no function in antigen presentation-are induced on the surface of pathogen-infected cells. We found that infection by cytomegalovirus (CMV) resulted in substantial increases in MIC on cultured fibroblast and endothelial cells and was associated with induced MIC expression in interstitial pneumonia. MIC engagement of **NKG2D** potently augmented T cell antigen receptor (TCR)-dependent cytolytic and cytokine responses by CMV-specific CD28-CD8alphabeta T cells. This function overcame viral interference with MHC class I antigen presentation. Combined triggering of TCR-CD3 complexes and **NKG2D** induced interleukin 2 production and T cell proliferation. Thus **NKG2D** functioned as a costimulatory receptor that can substitute for CD28.

L22 ANSWER 6 OF 18 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:410146 BIOSIS
DN PREV200100410146
TI Crystal structure of the murine NK cell-activating receptor **NKG2D** at 1.95 ANG.
AU Wolan, Dennis W.; Teyton, Luc; Rudolph, Markus G.; Villmow, Brigitte; Bauer, Stefan; Busch, Dirk H.; Wilson, Ian A. (1)
CS (1) Department of Molecular Biology, Skaggs Institute for Chemical Biology, Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA, 92037: dirk.busch@lrz.tum.de, wilson@scripps.edu USA
SO Nature Immunology, (March, 2001) Vol. 2, No. 3, pp. 248-254. print. ISSN: 1529-2908.
DT Article
LA English
SL English
AB **NKG2D**, a homodimeric lectin-like receptor, is a unique stimulatory molecule that is found on natural killer cells, T cells and activated macrophages. The natural **ligands** for murine **NKG2D** are distant major histocompatibility complex homologs, retinoic acid early transcript (Rae1) and H-60 minor histocompatibility antigen. The crystal structure of the extracellular region of murine **NKG2D** reveals close homology with other C-type lectin receptors such as CD94, Ly49A, rat MBP-A and CD69. However, the precise mode of dimeric assembly varies among these natural killer receptors, as well as their surface topography and electrostatic properties. The **NKG2D** structure provides the first structural insights into the role and **ligand** specificity of this stimulatory receptor in the innate and adaptive immune system.

L22 ANSWER 7 OF 18 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:454125 BIOSIS
DN PREV200100454125
TI Molecular competition for **NKG2D**: H60 and RAE1 compete unequally for **NKG2D** with dominance of H60.
AU O'Callaghan, Christopher A.; Cerwenka, Adelheid; Willcox, Benjamin E.; Lanier, Lewis L.; Bjorkman, Pamela J. (1)
CS (1) Howard Hughes Medical Institute, California Institute of Technology,

Pasadena, CA, 91125: bjorkman@its.caltech.edu USA
SO Immunity, (August, 2001) Vol. 15, No. 2, pp. 201-211. print.
ISSN: 1074-7613.
DT Article
LA English
SL English
AB **NKG2D** is a potent activating receptor on natural killer cells, T cells, and macrophages. Mouse **NKG2D** interacts with two cell surface **ligands** related to class I MHC molecules: RAE1 and H60. We used soluble versions of **NKG2D**, RAE1, and H60 to characterize their interactions. RAE1 and H60 each bind **NKG2D** with nanomolar affinities, indicating tighter binding than most cell surface immune interactions, but **NKG2D** binds to H60 with apprx25-fold higher affinity than to RAE1. RAE1 and H60 compete directly for occupancy of **NKG2D**, and, thus, **NKG2D** can be occupied by only one **ligand** at a time. The **NKG2D**-H60 interaction is more temperature dependent and makes greater use of electrostatic interactions than the **NKG2D**-RAE1 interaction. The distinct thermodynamic profiles provide insights into the different molecular mechanisms of the binding interactions.

L22 ANSWER 8 OF 18 HCAPLUS COPYRIGHT 2001 ACS DUPLICATE 3
AN 2001:659192 HCAPLUS
TI The UL16-binding proteins, a novel family of MHC class I-related **ligands** for **NKG2D**, activate natural killer cell functions
AU Sutherland, Claire L.; Chalupny, N. Jan; Cosman, David
CS Department of Molecular Biology, Immunex Corporation, Seattle, WA, 98101, USA
SO Immunol. Rev. (2001), 181, 185-192
CODEN: IMRED2; ISSN: 0105-2896
PB Munksgaard International Publishers Ltd.
DT Journal
LA English
AB The UL16-binding proteins (ULBPs) are a novel family of MHC class I-related mols. (MICs) that were identified based on their ability to bind to the human cytomegalovirus (HCMV) glycoprotein UL16. UL16 also binds to a member of another family of MHC class I-like mols., MICB. The ULBPs and MICs are ligands for **NKG2D**/DAP10, an activating receptor expressed by natural killer (NK) cells and other immune effector cells, and this interaction can be blocked by UL16. Engagement of **NKG2D** /DAP10 by ULBPs or MICs expressed on a target cell can overcome an inhibitory signal generated by NK-cell recognition of MHC class I mols. and trigger NK cytotoxicity. ULBPs elicit their effects on NK cells by activating the janus kinase 2, signal transducer and activator of transcription 5, extracellular-signal-regulated kinase mitogen-activated protein kinase and Akt/protein kinase B signal transduction pathways. Although ULBPs alone activate multiple signaling pathways and induce modest cytokine prodn., ULBPs synergize strongly with interleukin-12 for prodn. of interferon-.gamma. by NK cells. This finding is consistent with reports in T cells that **NKG2D**/DAP10 can act as a costimulatory receptor in a similar manner as CD28. The possible roles of ULBPs in mediating immune responses to viruses and tumors and the potential mechanisms by which UL16 may allow HCMV to evade immune detection are areas of active investigation.
RE.CNT 50
RE
(1) Azuma, M; J Immunol 1993, V150, P1147 HCAPLUS
(2) Bauer, S; Science 1999, V285, P727 HCAPLUS
(3) Biron, C; Annu Rev Immunol 1999, V17, P189 HCAPLUS
(5) Blery, M; Hum Immunol 2000, V61, P51 HCAPLUS
(6) Boise, L; Immunity 1995, V3, P87 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 9 OF 18 HCAPLUS COPYRIGHT 2001 ACS
AN 2001:707947 HCAPLUS
TI Rae1 and H60 **ligands** of the **NKG2D** receptor stimulate tumour immunity
AU Diefenbach, Andreas; Jansen, Eric R.; Jamison, Amanda M.; Raulet, David H.
CS Department of Molecular and Cell Biology and Cancer Research Lab., University of California, Berkeley, 94720, USA
SO Nature (London, U. K.) (2001), 413(6852), 165-171
CODEN: NATUAS; ISSN: 0028-0836
PB Nature Publishing Group
DT Journal
LA English
AB Natural killer (NK) cells attack many tumor cell lines, and are thought to have a crit. role in anti-tumor immunity; however, the interaction between NK cells and tumor targets is poorly understood. The stimulatory lectin-like **NKG2D** receptor is expressed by NK cells, activated CD8+ T cells and by activated macrophages in mice. Several distinct cell-surface ligands that are related to class I major histocompatibility complex mols. have been identified'1-1, some of which are expressed at high levels by tumor cells but not by normal cells in adults. However, no direct evidence links the expression of these 'induced self' ligands with tumor cell rejection. Here we demonstrate that ectopic expression of the murine **NKG2D** ligands Rae1.beta. or H60 in several tumor cell lines results in potent rejection of the tumor cells by syngeneic mice. Rejection is mediated by NK cells and/or CD8+ T cells. The ligand-expressing tumor cells induce potent priming of cytotoxic T cells and sensitization of NK cells in vivo. Mice that are exposed to live or irradiated tumor cells expressing Rae1 or H60 are specifically immune to subsequent challenge with tumor cells that lack **NKG2D** ligands, suggesting application of the ligands in the design of tumor vaccines.
RE.CNT 30
RE
(1) Bauer, S; Science 1999, V285, P727 HCAPLUS
(2) Cerwenka, A; Immunity 2000, V12, P721 HCAPLUS
(3) Cosman, D; Immunity 2001, V14, P123 HCAPLUS
(4) Diefenbach, A; Nature Immunol 2000, V1, P119 HCAPLUS
(5) Dranoff, G; Proc Natl Acad Sci 1993, V90, P3539 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 10 OF 18 HCAPLUS COPYRIGHT 2001 ACS
AN 2001:659190 HCAPLUS
TI **Ligands** for natural killer cell receptors: Redundancy or specificity
AU Cerwenka, Adelheid; Lanier, Lewis L.
CS Department of Microbiology and Immunology and the Cancer Research Institute, University of California, San Francisco, CA, 94143-0414, USA
SO Immunol. Rev. (2001), 181, 158-169
CODEN: IMRED2; ISSN: 0105-2896
PB Munksgaard International Publishers Ltd.
DT Journal
LA English
AB Several inhibitory and activating receptors involved in natural killer cell activation have been characterized. The increasing knowledge about their ligands, including classical MHC class I mols., non-classical MHC class I mols. and MHC class I-related mols., is shedding new light on the targets of innate immune recognition. While classical MHC class I mols. are constitutively expressed, some MHC class I-related (MIC) mols., however, are stress-induced by ill-defined stimuli. Two families of ligands for the human activating **NKG2D** receptor have been identified. These are the MIC proteins encoded by two highly polymorphic genes within the MHC class I and the retinoic acid-inducible early gene-1-like (also designated UL16-binding) proteins encoded by genes

outside the MHC. For the mouse **NKG2D** receptor, one family, contg. at least five distinct ligands, has been described. A better understanding about how targets signal their distress, which renders them susceptible to natural killer (NK)-cell attack, will help to define the role of NK cells in antimicrobial and antitumor immunity and transplantation.

RE.CNT 90
RE
(1) Bahram, S; Adv Immunol 2000, V76, P1 HCAPLUS
(2) Bahram, S; Proc Natl Acad Sci USA 1994, V91, P6259 HCAPLUS
(3) Bakker, A; Hum Immunol 2000, V61, P18 HCAPLUS
(4) Bakker, A; Immunity 2000, V13, P345 HCAPLUS
(5) Bauer, S; Science 1999, V285, P727 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 11 OF 18 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:141877 BIOSIS
DN PREV200100141877
TI ULBPs, Novel MHC class I-related molecules, bind to CMV glycoprotein UL16 and stimulate NK cytotoxicity through the **NKG2D** receptor.
AU Cosman, David (1); Mullberg, Jurgen; Sutherland, Claire L.; Chin, Wilson; Armitage, Richard; Fanslow, William; Kubin, Marek; Chalupny, N. Jan
CS (1) Department of Molecular Biology, Immunex Corporation, 51 University Street, Seattle, WA, 98101: cosman@immunex.com USA
SO Immunity, (February, 2001) Vol. 14, No. 2, pp. 123-133. print. ISSN: 1074-7613.
DT Article
LA English
SL English
AB The human cytomegalovirus glycoprotein, UL16, binds to two members of a novel family of molecules, the ULBPs, and to the MHC class I homolog, MICB. The ULBPs are GPI-linked glycoproteins belonging to the extended MHC class I family but are only distantly related to MICB. The ULBP and MICB molecules are **ligands** for the activating receptor, **NKG2D** /DAP10, and this interaction is blocked by a soluble form of UL16. The ULBPs stimulate cytokine and chemokine production from NK cells, and expression of ULBPs in NK cell-resistant target cells confers susceptibility to NK cell cytotoxicity. Masking of NK cell recognition of ULBP or MIC antigens by UL16 provides a potential mechanism by which human cytomegalovirus-infected cells might evade attack by the immune system.

L22 ANSWER 12 OF 18 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:106283 BIOSIS
DN PREV200100106283
TI Triggering receptors involved in natural killer cell-mediated cytotoxicity against choriocarcinoma cell lines.
AU Sivori, Simona; Parolini, Silvia; Marcenaro, Emanuela; Millo, Romano; Bottino, Cristina; Moretta, Alessandro (1)
CS (1) Dipartimento di Medicina Sperimentale, Sezione di Istologia, Universita di Genova, Via G.B. Marsano 10, 16132, Genova: alemoret@unige.it/bottino@ermes.cba.unige.it Italy
SO Human Immunology, (November, 2000) Vol. 61, No. 11, pp. 1055-1058. print. ISSN: 0198-8859.
DT Article
LA English
SL English
AB The lack of classical HLA-class I molecules on trophoblast is necessary to prevent allorecognition by maternal CTL, but may induce activation of NK cells. A protective role against NK cells equipped of suitable inhibitory receptors has been proposed for nonclassical HLA-class I molecules including HLA-E and HLA-G. In the present study we show that the NK-mediated killing of two choriocarcinoma cell lines, JAR and JEG3, is induced upon engagement of natural cytotoxicity receptors (NCR) with their

specific **ligands**. In particular, we show that NKp44, a triggering receptor expressed at the NK cell surface only after in vitro culture in the presence of IL-2, plays a central role in triggering NK cytotoxicity against trophoblast cells. Also NKp46 appear to contribute to this function by cooperating with NKp44. On the other hand, other triggering receptors such as NKp30, 2B4, and **NKG2D** are not involved in killing of choriocarcinoma. Our findings suggest that resistance of trophoblast to NK-mediated cytotoxicity is the result of insufficient activating interactions between the various triggering NK receptors and their target cell **ligands**. On the other hand, the interaction of nonclassical HLA class I molecules with inhibitory NK receptors appears to play only a marginal role in regulating the susceptibility of choriocarcinoma to NK mediated cytotoxicity.

L22 ANSWER 13 OF 18 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:385618 BIOSIS
DN PREV200100385618
TI Human natural killer cell activating receptors.
AU Biassoni, Roberto (1); Cantoni, Claudia; Falco, Michela; Pende, Daniela; Millo, Romano; Moretta, Lorenzo; Bottino, Cristina; Moretta, Alessandro
CS (1) Istituto Nazionale per la Ricerca sul Cancro, Laboratorio di Immunologia, IST/CBA, L.go R. Benzi, 10, 16132, Genova: biassoni@cba.unige.it Italy
SO Molecular Immunology, (December, 2000) Vol. 37, No. 17, pp. 1015-1024. print.
ISSN: 0161-5890.
DT General Review
LA English
SL English
AB Natural killer (NK) cells were poorly characterized until 10 years ago and few molecules expressed on their cell surface were known. Now the situation has changed dramatically, since a plethora of receptors characterized by opposite functions have been functionally and molecularly defined. NK cells express clonally distributed inhibitory receptors specific for different groups of HLA class I alleles, thus protecting normal cells from NK-mediated lysis. On the contrary, various activating receptors are involved in triggering of NK-mediated natural cytotoxicity. Their engagement induces human NK cells to kill target cells that are either HLA class I-negative or -deficient. Here a brief description of the activating receptors and coreceptor and of their **ligand**(s) is given.

L22 ANSWER 14 OF 18 HCAPLUS COPYRIGHT 2001 ACS DUPLICATE 4
AN 2000:472382 HCAPLUS
DN 133:191846
TI Retinoic acid early inducible genes define a **ligand** family for the activating **NKG2D** receptor in mice
AU Cerwenka, Adelheid; Bakker, Alexander B. H.; McClanahan, Terri; Wagner, Janet; Wu, Jun; Phillips, Joseph H.; Lanier, Lewis L.
CS Department of Microbiology and Immunology and The Cancer Research Institute, University of California, San Francisco, San Francisco, CA, 94143, USA
SO Immunity (2000), 12(6), 721-727
CODEN: IUNIEH; ISSN: 1074-7613
PB Cell Press
DT Journal
LA English
AB Here we describe a family of GPI-anchored cell surface proteins that function as ligands for the mouse activating **NKG2D** receptor. These mols. are encoded by the retinoic acid early inducible (RAE-1) and H60 minor histocompatibility antigen genes on mouse chromosome 10 and show weak homol. with MHC class I. Expression of the **NKG2D** ligands is low or absent on normal, adult tissues; however, they are

constitutively expressed on some tumors and upregulated by retinoic acid. Ectopic expression of RAE-1 and H60 confers target susceptibility to NK cell attack. These studies identify a family of ligands for the activating **NKG2D** receptor on NK and T cells, which may play an important role in innate and adaptive immunity.

RE.CNT 32
RE
(1) Aldrich, C; Cell 1994, V79, P649 HCAPLUS
(2) Bahram, S; Res Imunol 1996, V147, P328 HCAPLUS
(3) Bakker, A; Hum Immunol 2000, V61, P18 HCAPLUS
(4) Bauer, S; Science 1999, V285, P727 HCAPLUS
(5) Berg, S; Int Immunol 1998, V10, P379 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 15 OF 18 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:114379 BIOSIS
DN PREV200000114379
TI Paired inhibitory and triggering NK cell receptors for HLA class I molecules.
AU Lopez-Botet, Miguel (1); Bellon, Teresa; Llano, Manuel; Navarro, Francisco; Garcia, Pilar; de Miguel, Maria
CS (1) Servicio de Inmunologia, Hospital Universitario de la Princesa, Diego de Leon 62, 28006, Madrid Spain
SO Human Immunology, (Jan., 2000) Vol. 61, No. 1, pp. 7-17.
ISSN: 0198-8859.
DT Article
LA English
SL English
AB Human natural killer (NK) cells specifically interact with major histocompatibility complex (MHC) class I molecules employing different receptor systems, shared with subsets of alphabeta and gammadelta T lymphocytes. Killer cell immunoglobulin-like receptors (KIRs) recognize groups of human leukocyte antigen (HLA) class Ia proteins displaying common structural features at the alpha-1 domain; among them, KIR2DL4 has been proposed to specifically interact with the class Ib molecule HLA-G1. Members of a related family of immunoglobulin (Ig)-like receptors (ILT2 or LIR-1 and ILT4 or LIR-2), expressed by other leukocyte lineages, interact with a broad spectrum of class Ia molecules and HLA-G1. On the other hand, CD94/NKG2-A(-C) and **NKG2D** lectin-like receptors, respectively, recognize the class Ib molecules HLA-E and MICA. A recurrent finding within the different receptor families is the existence of pairs of homologous molecules that often share the same **ligands** but display divergent functions. Inhibitory receptors tend to exhibit an affinity for HLA molecules higher than their activating counterparts. Recruitment of SH2 domain-bearing tyrosine phosphatases (SHP) by cytoplasmic phosphorylated immunoreceptor tyrosine-based inhibition motifs (ITIMs) is a crucial event for the inhibitory signalling pathway. By contrast, triggering receptors assemble with homodimers of immune tyrosine-based activation motif (ITAM)-bearing adaptor molecules (i.e., DAP12, CD3 zeta) that engage tyrosine kinases (ZAP70 and syk). Human Immunology 61, 7-17 (2000).

L22 ANSWER 16 OF 18 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:765800 HCAPLUS
DN 132:62755
TI Natural killer cells: stress out, turn on, tune in
AU Diefenbach, Andreas; Raulet, David H.
CS Department of Molecular and Cell Biology and Cancer Research Laboratory, University of California at Berkeley, Berkeley, CA, 94720-3200, USA
SO Curr. Biol. (1999), 9(22), R851-R853
CODEN: CUBLE2; ISSN: 0960-9822
PB Current Biology Publications
DT Journal; General Review

LA English
AB A review with 14 refs. Natural killer cells attack tumor cells, infected cells and some normal cells, but the basis of their specificity is not completely understood. Recent studies indicate that epithelial tumor cells upregulate a stress-induced MHC class-I-like protein termed MICA, triggering NK cells via a recently described receptor called **NKG2D**

RE.CNT 14
RE
(1) Bahram, S; Proc Natl Acad Sci USA 1994, V91, P6259 HCAPLUS
(2) Bauer, S; Science 1999, V285, P727 HCAPLUS
(3) Correa, I; Eur J Immunol 1994, V24, P1323 HCAPLUS
(4) Groh, V; Proc Natl Acad Sci USA 1996, V93, P12445 HCAPLUS
(5) Groh, V; Proc Natl Acad Sci USA 1999, V96, P6879 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 17 OF 18 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1998:433707 BIOSIS
DN PREV199800433707
TI The genomic organization of NKG2C, E, F, and D receptor genes in the human natural killer gene complex.
AU Glienke, Jens; Sobanov, Yuri; Brostjan, Christine; Steffens, Christian; Nguyen, Catherine; Lehrach, Hans; Hofer, Erhard (1); Francis, Fiona
CS (1) Dep. Vascular Biol. Thrombosis Res., Univ. Vienna, Brunnerstr. 59, A-1235 Vienna Austria
SO Immunogenetics, (Aug., 1998) Vol. 48, No. 3, pp. 163-173.
ISSN: 0093-7711.
DT Article
LA English
AB Interactions of natural killer cell receptors with their cognate **ligands** play a major role in regulating NK cell function. The NKG2 gene family encodes several highly similar proteins, which are known to form heterodimers with the CD94 receptor. These dimers play a role in the inhibition as well as the activation of NK cells. We have analyzed the gene structures of the NKG2C, D, E, and F genes, and determined their genomic organization. Restriction mapping and sequencing revealed the four genes to be closely linked to one another, and of the same transcriptional orientation. An exon duplication within the NKG2C and E genes was identified, although the duplicated version of this exon has not yet been found in mRNA sequences. The NKG2C, E, and F genes, despite being highly similar, are variable at their 3' ends. We show that NKG2C consists of six exons, whereas NKG2E has seven, and the splice acceptor site for the seventh exon occurs in an Alu repeat. NKG2F consists of only four exons and part of exon IV is in some cases spliced to the 5' end of the **NKG2D** transcript. **NKG2D** has only a low similarity to the other NKG2 genes.

L22 ANSWER 18 OF 18 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1998:78276 BIOSIS
DN PREV199800078276
TI Cloning of a mouse homolog of CD94 extends the family of C-type lectins on murine natural killer cells.
AU Vance, Russell E.; Tanamachi, Dawn M.; Hanke, Thomas; Raulet, David H. (1)
CS (1) Dep. Mol. Cell Biol., Cancer Res. Lab., 485 LSA, Univ. Calif. at Berkeley, Berkeley, CA 94720 USA
SO European Journal of Immunology, (Dec., 1997) Vol. 27, No. 12, pp. 3236-3241.
ISSN: 0014-2980.
DT Article
LA English
AB Two families of major histocompatibility complex (MHC) class I-specific receptors are found on natural killer (NK) cells: immunoglobulin-like receptors and C-type lectin receptors. In mice, the latter category is

represented by the Ly49 family of receptors, whereas in humans, NK cells express the distantly related CD94, which forms MHC class I-specific heterodimers with NKG2 family members. Humans also express the MHC class I-specific p50/p58/p70 family of immunoglobulin-like receptors, but these have not been identified in mice. Hence, there is no known instance of an MHC class I-specific receptor that is expressed by both human and murine NK cells. Here we report the cloning of CD94 from the CB.17 and C57BL/6 strains of mice. Mouse CD94 is 54% identical and 66% similar to human CD94, and is also a member of the C-type lectin superfamily. Mouse CD94 is expressed efficiently on the cell surface of cells transiently transfected with the corresponding cDNA, but surface CD94 was unable to mediate detectable binding to MHC class I-expressing ConA blasts. Notably, mouse CD94, like human CD94, has a very short cytoplasmic tail, suggesting the existence of partner chains that may play a role in **ligand** binding and signaling. Like many other C-type lectins expressed by NK cells, mouse CD94 maps to the NK complex on distal chromosome 6, synteneic to human CD94. We also demonstrate that mouse CD94 is highly expressed specifically by mouse NK cells, raising the possibility that mice, like humans, express multiple families of MHC class I-specific receptors on their NK cells. Murine homologs of human NKG2 family members have not yet been identified, but we report here the existence of a murine **NKG2D**-like sequence that also maps to the murine NK complex near CD94 and Ly49 family members.

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=> fil wpids
FILE 'WPIDS' ENTERED AT 13:55:42 ON 15 NOV 2001
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    SEE http://www.derwent.com/dwpi/updates/dwpicov/index.html <<<

=> d que l15
L15           1 SEA FILE=WPIDS ABB=ON  NKG2D OR NKG2 D


=> d bib ab tech l15

L15  ANSWER 1 OF 1  WPIDS COPYRIGHT 2001   DERWENT INFORMATION LTD
AN   1992-365992 [44]   WPIDS
DNC  C1992-162471
TI   Isolated DNA or CDNA sequence encoding extracellular part of
     trans-membrane protein - used as immunosuppressants in organ transplants,
     and for treating auto-immune diseases, cancer and viral infections, also
     useful in diagnosis.
DC   B04 D16
IN   BACH, F H; HOFER, E; HOUCHINS, J P; MCSHERRY, C M; YABE, T S; YABE, T
PA   (SANO) SANDOZ LTD; (MINU) UNIV MINNESOTA; (NOVS) NOVARTIS AG
CYC  17
PI   WO 9217198    A1 19921015 (199244)* EN   62p
        RW: AT BE CH DE DK ES FR GB GR IT LU MC NL SE
         W: JP US
     EP 585257     A1 19940309 (199410)  EN
         R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
     JP 06506358   W  19940721 (199433)       15p
     EP 585257     A4 19950222 (199611)
     US 6262244    B1 20010717 (200148)
ADT  WO 9217198 A1 WO 1992-US2469 19920327; EP 585257 A1 EP 1992-909331
     19920327, WO 1992-US2469 19920327; JP 06506358 W JP 1992-508930 19920327,
     WO 1992-US2469 19920327; EP 585257 A4 EP 1992-909331         ; US 6262244
     B1 CIP of US 1991-676663 19910328, Cont of WO 1992-US2469 19920327, Cont
     of US 1993-122514 19930924, US 1995-543246 19951013
FDT  EP 585257 A1 Based on WO 9217198; JP 06506358 W Based on WO 9217198
PRAI US 1991-676663   19910328; US 1993-122514   19930924; US 1995-543246
     19951013
AB   WO   9217198 A UPAB: 19931116
     In an isolated DNA or cDNA encoding the extracellular part of a
     transmembrane protein designated (a) NKG2-A, (b) NKG2-B, (c) NKG2-C and
     (d) NKG2-D (f = fragment) translated in natural killer
     cells or T-cells, the DNA is selected from portions of DNA sequences in
     the specification.
          Also new are (a) isolated DNA or cDNA encoding a complete
     transmembrane protein designated nKG2-A NKG2-B, NKG2-C and NKG2-
     D (in specification); (b) isolated extracellular part, or the
     complete transmembrane protein (in specification), or sequence variants;
```

(c) poly- or monoclonal antibody recognising at least one epitope of (b); (d) bifunctional antibody recognising at least one epitope of (b) and a cancer- of virus-specific antigen; and (e) a chimeric protein mol. comprising (b) and a cytotoxic protein.

USE/ADVANTAGE - The DNA or chimeric protein may be used to treat a cancer or virus infection. Antibodies can activate natural killer cells and T-cells. The extracellular domains of the proteins are useful diagnostic tools for detecting target ligands, e.g. carbohydrate groups present on some cancer and virus-infected cells, and the complete protein may be used to study the mechanism of natural killer cell regulation. Dwg.0/1

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=> fil medline
FILE 'MEDLINE' ENTERED AT 14:14:40 ON 15 NOV 2001

 FILE LAST UPDATED: 14 NOV 2001 (20011114/UP). FILE COVERS 1958 TO DATE.

 On April 22, 2001, MEDLINE was reloaded. See HELP RLOAD for details.

 MEDLINE now contains IN-PROCESS records. See HELP CONTENT for details.

 MEDLINE is now updated 4 times per week. A new current-awareness alert
 frequency (EVERYUPDATE) is available. See HELP UPDATE for more information.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2001 vocabulary. Enter HELP THESAURUS for details.

 The OLDMEDLINE file segment now contains data from 1958 through 1965.
 Enter HELP CONTENT for details.

 Left, right, and simultaneous left and right truncation are available in the
 Basic Index. See HELP SFIELDS for details.

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 SUBSTANCE IDENTIFICATION.

=> d his


     (FILE 'HOME' ENTERED AT 14:13:18 ON 15 NOV 2001)

     FILE 'MEDLINE' ENTERED AT 14:13:24 ON 15 NOV 2001
L1            47 S NKG2D OR NKG2 D
L2         23939 S LIGANDS/CT
L3        101218 S RECEPTORS, IMMUNOLOGIC+NT/CT
L4            11 S L1 AND L2
L5            11 S L4 AND L3
L6        546911 S TUMOR#
L7            13 S L1 AND L6
L8             7 S L7 NOT L5

     FILE 'MEDLINE' ENTERED AT 14:14:40 ON 15 NOV 2001

=> d .med 15 1-11;d .med 18 1-7

L5   ANSWER 1 OF 11     MEDLINE
AN   2001510266     MEDLINE
DN   21441910   PubMed ID: 11557981
TI   Rae1 and H60 ligands of the NKG2D receptor stimulate tumour
     immunity.
AU   Diefenbach A; Jensen E R; Jamieson A M; Raulet D H
CS   Department of Molecular and Cell Biology and Cancer Research Laboratory,
     University of California, Berkeley 94720, USA.
SO   NATURE, (2001 Sep 13) 413 (6852) 165-71.
     Journal code: NSC; 0410462. ISSN: 0028-0836.
CY   England: United Kingdom
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   200110
ED   Entered STN: 20010917
     Last Updated on STN: 20011022
     Entered Medline: 20011018
AB   Natural killer (NK) cells attack many tumour cell lines, and are thought
     to have a critical role in anti-tumour immunity; however, the interaction
```

between NK cells and tumour targets is poorly understood. The stimulatory lectin-like **NKG2D** receptor is expressed by NK cells, activated CD8+ T cells and by activated macrophages in mice. Several distinct cell-surface ligands that are related to class I major histocompatibility complex molecules have been identified, some of which are expressed at high levels by tumour cells but not by normal cells in adults. However, no direct evidence links the expression of these 'induced self' ligands with tumour cell rejection. Here we demonstrate that ectopic expression of the murine **NKG2D** ligands Rae1beta or H60 in several tumour cell lines results in potent rejection of the tumour cells by syngeneic mice. Rejection is mediated by NK cells and/or CD8+ T cells. The ligand-expressing tumour cells induce potent priming of cytotoxic T cells and sensitization of NK cells in vivo. Mice that are exposed to live or irradiated tumour cells expressing Rae1 or H60 are specifically immune to subsequent challenge with tumour cells that lack **NKG2D** ligands, suggesting application of the ligands in the design of tumour vaccines.

CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
*CD8-Positive T-Lymphocytes: IM, immunology
Cytotoxicity, Immunologic
Immunity
*Killer Cells, Natural: IM, immunology
Ligands
*Membrane Proteins: ME, metabolism
Mice
Mice, Inbred C57BL
*Minor Histocompatibility Antigens: ME, metabolism
*Neoplasms: IM, immunology
***Receptors, Immunologic: ME, metabolism**
Recombinant Proteins
T-Lymphocytes, Cytotoxic: IM, immunology
Tumor Cells, Cultured

L5 ANSWER 2 OF 11 MEDLINE
AN 2001445970 MEDLINE
DN 21383614 PubMed ID: 11491531
TI Interactions of human **NKG2D** with its ligands MICA, MICB, and homologs of the mouse RAE-1 protein family.
AU Steinle A; Li P; Morris D L; Groh V; Lanier L L; Strong R K; Spies T
CS Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle WA 98109, USA.
NC AI30581 (NIAID)
AI42200 (NIAID)
SO IMMUNOGENETICS, (2001 May-Jun) 53 (4) 279-87.
Journal code: GI4; 0420404. ISSN: 0093-7711.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200108
ED Entered STN: 20010813
Last Updated on STN: 20010827
Entered Medline: 20010823

AB **NKG2D** is an activating receptor that is expressed on most natural killer (NK) cells, CD8 alphabeta T cells, and gammadelta T cells. Among its ligands is the distant major histocompatibility complex class I homolog MICA, which has no function in antigen presentation but is induced by cellular stress. To extend previous functional evidence, the **NKG2D**-MICA interaction was studied in isolation. **NKG2D** homodimers formed stable complexes with monomeric MICA in solution, demonstrating that no other components were required to facilitate this interaction. MICA glycosylation was not essential but enhanced complex formation. Soluble **NKG2D** also bound to cell surface MICB, which has structural and functional properties similar to those of MICA.

Moreover, **NKG2D** stably interacted with surface molecules encoded by three newly identified cDNA sequences (N2DL-1, -2, and -3), which are identical to the human ULBP proteins and may represent homologs of the mouse retinoic acid-early inducible family of **NKG2D** ligands. Because of the substantial sequence divergence among these molecules, these results indicated promiscuous modes of receptor binding. Comparison of allelic variants of MICA revealed large differences in **NKG2D** binding that were associated with a single amino acid substitution at position 129 in the alpha2 domain. Varying affinities of MICA alleles for **NKG2D** may affect thresholds of NK-cell triggering and T-cell modulation.

CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Amino Acid Sequence
Antigens, Surface: ME, metabolism
Dimerization
Histocompatibility Antigens Class I: CH, chemistry
*Histocompatibility Antigens Class I: ME, metabolism
*Killer Cells, Natural: IM, immunology
Ligands
*Membrane Proteins: ME, metabolism
Models, Molecular
Molecular Sequence Data
Protein Binding
***Receptors, Immunologic: ME, metabolism**
Sequence Homology, Amino Acid
Solubility

L5 ANSWER 3 OF 11 MEDLINE
AN 2001373026 MEDLINE
DN 21323007 PubMed ID: 11429322
TI MICA and MICB genes: can the enigma of their polymorphism be resolved?.
AU Stephens H A
CS Institute of Urology and Nephrology, University College London, The Middlesex Hospital, 48 Riding House Street, London, UK, W1W 7EY.. h.stephens@ucl.ac.uk
SO Trends Immunol, (2001 Jul) 22 (7) 378-85. Ref: 72
Journal code: DZX; 100966032. ISSN: 1471-4906.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200108
ED Entered STN: 20010903
Last Updated on STN: 20010903
Entered Medline: 20010830
AB The human MHC class I chain-related genes (MICA and MICB) are located within the HLA class I region of chromosome 6. Their organization, expression and products differ considerably from classical HLA class I genes. MIC proteins are considered to be markers of "stress" in the epithelia, and act as ligands for cells expressing a common activatory natural killer-cell receptor (**NKG2D**). Molecular models are now available for the MICA protein, both bound and complexed with **NKG2D**. MICA molecules appear to be highly flexible and polymorphic, although the functional relevance and implications of their polymorphism have yet to be fully discerned.
CT Check Tags: Animal; Human; Support, Non-U.S. Gov't
Alleles
Chromosome Mapping
Epithelial Cells
Evolution, Molecular
Gene Expression

Genetics, Population
*Histocompatibility Antigens Class I: GE, genetics
Histocompatibility Antigens Class I: IM, immunology
Killer Cells, Natural: IM, immunology
Ligands
*Polymorphism (Genetics)
Receptors, Immunologic: IM, immunology

L5 ANSWER 4 OF 11 MEDLINE
AN 2001309272 MEDLINE
DN 21223631 PubMed ID: 11323699
TI Complex structure of the activating immunoreceptor **NKG2D** and its MHC class I-like ligand MICA.
CM Comment in: Nat Immunol. 2001 May;2(5):379-80
AU Li P; Morris D L; Willcox B E; Steinle A; Spies T; Strong R K
CS Division of Basic Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA 98109 USA.
NC AI30581 (NIAID)
AI42200 (NIAID)
CA18221 (NCI)
SO Nat Immunol, (2001 May) 2 (5) 443-51.
Journal code: D0G; 100941354. ISSN: 1529-2908.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200105
ED Entered STN: 20010604
Last Updated on STN: 20010604
Entered Medline: 20010531
AB The major histocompatibility complex (MHC) class I homolog, MICA, is a stress-inducible ligand for **NKG2D**, a C-type lectin-like activating immunoreceptor. The crystal structure of this ligand-receptor complex that we report here reveals an **NKG2D** homodimer bound to a MICA monomer in an interaction that is analogous to that seen in T cell receptor-MHC class I protein complexes. Similar surfaces on each **NKG2D** monomer interact with different surfaces on either the alpha1 or alpha2 domains of MICA. The binding interactions are large in area and highly complementary. The central section of the alpha2-domain helix, disordered in the structure of MICA alone, is ordered in the complex and forms part of the **NKG2D** interface. The extensive flexibility of the interdomain linker of MICA is shown by its altered conformation when crystallized alone or in complex with **NKG2D**.
CT Check Tags: Human; Support, U.S. Gov't, P.H.S.
Amino Acid Sequence
*Histocompatibility Antigens Class I: CH, chemistry
*Killer Cells, Natural: IM, immunology
Lectins: CH, chemistry
Ligands
Models, Molecular
Molecular Sequence Data
Protein Binding
Protein Conformation
***Receptors, Immunologic: CH, chemistry**
Sequence Homology, Amino Acid
Surface Plasmon Resonance
Surface Properties

L5 ANSWER 5 OF 11 MEDLINE
AN 2001216034 MEDLINE
DN 21205390 PubMed ID: 11248803
TI Ligands for the murine **NKG2D** receptor: expression by tumor cells and activation of NK cells and macrophages.

CM Comment in: Nat Immunol. 2000 Aug;1(2):95-7
AU Diefenbach A; Jamieson A M; Liu S D; Shastri N; Raulet D H
CS Department of Molecular and Cell Biology and Cancer Research Laboratory, University of California, Berkeley, USA.
SO Nat Immunol, (2000 Aug) 1 (2) 119-26.
Journal code: D0G; 100941354. ISSN: 1529-2908.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200105
ED Entered STN: 20010521
Last Updated on STN: 20010521
Entered Medline: 20010517
AB Natural killer (NK) cells attack tumor and infected cells, but the receptors and ligands that stimulate them are poorly understood. Here we report the expression cloning of two murine ligands for the lectin-like receptor **NKG2D**. The two ligands, H-60 and Rae1 beta, are distant relatives of major histocompatibility complex class I molecules. **NKG2D** ligands are not expressed by most normal cells but are up-regulated on numerous tumor cells. We show that mouse **NKG2D** is expressed by NK cells, activated CD8+ T cells and activated macrophages. Expression of either **NKG2D** ligand by target cells triggers NK cell cytotoxicity and interferon-gamma secretion by NK cells, as well as nitric oxide release and tumor necrosis factor alpha transcription by macrophages. Thus, through their interaction with **NKG2D**, H-60 and Rae1 beta are newly identified potent stimulators of innate immunity.
CT Check Tags: Animal; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
CHO Cells
COS Cells
Cercopithecus aethiops
Cloning, Molecular
Hamsters
*Killer Cells, Natural: IM, immunology
Killer Cells, Natural: ME, metabolism
Ligands
Lymphocyte Transformation
Macrophage Activation
*Macrophages, Peritoneal: IM, immunology
Macrophages, Peritoneal: ME, metabolism
Membrane Proteins: GE, genetics
*Membrane Proteins: IM, immunology
Mice
Mice, Inbred BALB C
Mice, Inbred C57BL
Minor Histocompatibility Antigens: GE, genetics
*Minor Histocompatibility Antigens: IM, immunology
Receptors, Immunologic: GE, genetics
***Receptors, Immunologic: ME, metabolism**
Tumor Cells, Cultured

L5 ANSWER 6 OF 11 MEDLINE
AN 2001210233 MEDLINE
DN 21195294 PubMed ID: 11298332
TI Role of **NKG2D** in tumor cell lysis mediated by human NK cells: cooperation with natural cytotoxicity receptors and capability of recognizing tumors of nonepithelial origin.
AU Pende D; Cantoni C; Rivera P; Vitale M; Castriconi R; Marcenaro S; Nanni M; Biassoni R; Bottino C; Moretta A; Moretta L
CS Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy.
SO EUROPEAN JOURNAL OF IMMUNOLOGY, (2001 Apr) 31 (4) 1076-86.

Journal code: EN5; 1273201. ISSN: 0014-2980.
CY Germany: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200105
ED Entered STN: 20010517
Last Updated on STN: 20010517
Entered Medline: 20010510
AB **NKG2D** is a recently described activating receptor expressed by both NK cells and CTL. In this study we investigated the role of **NKG2D** in the natural cytolysis mediated by NK cell clones. The role of **NKG2D** varied depending on the type of target cells analyzed. Lysis of various tumors appeared to be exclusively natural cytotoxicity receptors (NCR) dependent. In contrast, killing of another group of target cells, including not only the epithelial cell lines HELA and IGROV-1, but also the FO-1 melanoma, the JA3 leukemia, the Daudi Burkitt lymphoma and even normal PHA-induced lymphoblasts, involved both NCR and **NKG2D**. Notably, NK cell clones expressing low surface densities of NCR (NCR(dull)) could lyse these tumors in an exclusively **NKG2D**-dependent fashion. Remarkably, not all of these targets expressed MICA/B, thus implying the existence of additional ligands recognized by **NKG2D**, possibly represented by GPI-linked molecules. Finally, we show that the engagement of different HLA class I-specific inhibitory receptors by either specific antibodies or the appropriate HLA class I ligand led to inhibition of **NKG2D** -mediated NK cell triggering.
CT Check Tags: Animal; Human; Support, Non-U.S. Gov't
Antibodies, Monoclonal: IM, immunology
Antibodies, Monoclonal: PD, pharmacology
Cells, Cultured
Clone Cells: DE, drug effects
Clone Cells: IM, immunology
*Cytotoxicity, Immunologic
Cytotoxicity, Immunologic: DE, drug effects
Down-Regulation (Physiology)
Epithelial Cells: IM, immunology
Epithelial Cells: PA, pathology
Flow Cytometry
Histocompatibility Antigens Class I: IM, immunology
Killer Cells, Natural: DE, drug effects
*Killer Cells, Natural: IM, immunology
Killer Cells, Natural: ME, metabolism
Ligands
Mice
*Neoplasms: IM, immunology
*Neoplasms: PA, pathology
Phytohemagglutinins: IM, immunology
Phytohemagglutinins: PD, pharmacology
RNA, Messenger: AN, analysis
RNA, Messenger: GE, genetics
Receptors, Immunologic: GE, genetics
***Receptors, Immunologic: IM, immunology**
Transfection
Tumor Cells, Cultured

L5 ANSWER 7 OF 11 MEDLINE
AN 2001205813 MEDLINE
DN 21137928 PubMed ID: 11239445
TI ULBPs, novel MHC class I-related molecules, bind to CMV glycoprotein UL16 and stimulate NK cytotoxicity through the **NKG2D** receptor.
AU Cosman D; Mullberg J; Sutherland C L; Chin W; Armitage R; Fanslow W; Kubin M; Chalupny N J

CS Department of Molecular Biology, Immunex Corporation, 51 University Street, Seattle, WA 98101,. USA.cosman@immunex.com
SO IMMUNITY, (2001 Feb) 14 (2) 123-33.
Journal code: CCF; 9432918. ISSN: 1074-7613.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-AF304377; GENBANK-AF304378; GENBANK-AF304379
EM 200104
ED Entered STN: 20010417
Last Updated on STN: 20010417
Entered Medline: 20010412
AB The human cytomegalovirus glycoprotein, UL16, binds to two members of a novel family of molecules, the ULBPs, and to the MHC class I homolog, MICB. The ULBPs are GPI-linked glycoproteins belonging to the extended MHC class I family but are only distantly related to MICB. The ULBP and MICB molecules are ligands for the activating receptor, **NKG2D**/DAP10, and this interaction is blocked by a soluble form of UL16. The ULBPs stimulate cytokine and chemokine production from NK cells, and expression of ULBPs in NK cell-resistant target cells confers susceptibility to NK cell cytotoxicity. Masking of NK cell recognition of ULBP or MIC antigens by UL16 provides a potential mechanism by which human cytomegalovirus-infected cells might evade attack by the immune system.
CT Check Tags: Human
Amino Acid Sequence
Base Sequence
Carrier Proteins: GE, genetics
*Carrier Proteins: IM, immunology
*Carrier Proteins: ME, metabolism
Cell Line
*Cytomegalovirus: IM, immunology
*Cytomegalovirus: ME, metabolism
Cytomegalovirus: PY, pathogenicity
Cytotoxicity, Immunologic
DNA Primers: GE, genetics
Glycoproteins: IM, immunology
Glycoproteins: ME, metabolism
Histocompatibility Antigens Class I: GE, genetics
*Histocompatibility Antigens Class I: IM, immunology
*Histocompatibility Antigens Class I: ME, metabolism
*Killer Cells, Natural: IM, immunology
Ligands
Molecular Sequence Data
***Receptors, Immunologic: ME, metabolism**
Sequence Homology, Amino Acid
*Viral Proteins: IM, immunology
*Viral Proteins: ME, metabolism

L5 ANSWER 8 OF 11 MEDLINE
AN 2000350669 MEDLINE
DN 20350669 PubMed ID: 10894171
TI Retinoic acid early inducible genes define a ligand family for the activating **NKG2D** receptor in mice.
AU Cerwenka A; Bakker A B; McClanahan T; Wagner J; Wu J; Phillips J H; Lanier L L
CS Department of Microbiology and Immunology and The Cancer Research Institute, University of California, San Francisco 94143, USA.
SO IMMUNITY, (2000 Jun) 12 (6) 721-7.
Journal code: CCF; 9432918. ISSN: 1074-7613.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English

FS Priority Journals
OS GENBANK-AF257520
EM 200007
ED Entered STN: 20000811
Last Updated on STN: 20000811
Entered Medline: 20000731
AB Here we describe a family of GPI-anchored cell surface proteins that function as ligands for the mouse activating **NKG2D** receptor. These molecules are encoded by the retinoic acid early inducible (RAE-1) and H60 minor histocompatibility antigen genes on mouse chromosome 10 and show weak homology with MHC class I. Expression of the **NKG2D** ligands is low or absent on normal, adult tissues; however, they are constitutively expressed on some tumors and upregulated by retinoic acid. Ectopic expression of RAE-1 and H60 confers target susceptibility to NK cell attack. These studies identify a family of ligands for the activating **NKG2D** receptor on NK and T cells, which may play an important role in innate and adaptive immunity.
CT Check Tags: Animal; Human; Support, Non-U.S. Gov't
Amino Acid Sequence
Carcinoma, Lewis Lung
Cloning, Molecular: MT, methods
Cytotoxicity, Immunologic: DE, drug effects
Gene Expression Regulation: DE, drug effects
*Gene Expression Regulation: IM, immunology
Glycosylphosphatidylinositols: ME, metabolism
IgG: GE, genetics
Immunoglobulins, Fc: GE, genetics
Killer Cells, Natural: IM, immunology
*Killer Cells, Natural: ME, metabolism
Ligands
Membrane Proteins: BI, biosynthesis
*Membrane Proteins: GE, genetics
Membrane Proteins: ME, metabolism
Membrane Proteins: PH, physiology
Mice
Mice, Inbred C57BL
Minor Histocompatibility Antigens: BI, biosynthesis
Minor Histocompatibility Antigens: GE, genetics
Minor Histocompatibility Antigens: ME, metabolism
Minor Histocompatibility Antigens: PH, physiology
Molecular Sequence Data
*Multigene Family: IM, immunology
Receptors, Immunologic: GE, genetics
***Receptors, Immunologic: ME, metabolism**
Recombinant Fusion Proteins: GE, genetics
Recombinant Fusion Proteins: ME, metabolism
*Tretinoin: PD, pharmacology
Tumor Cells, Cultured

L5 ANSWER 9 OF 11 MEDLINE
AN 2000122083 MEDLINE
DN 20122083 PubMed ID: 10658973
TI Paired inhibitory and triggering NK cell receptors for HLA class I molecules.
AU Lopez-Botet M; Bellon T; Llano M; Navarro F; Garcia P; de Miguel M
CS Servicio de Immunologia, Hospital Universitario de la Princesa, Madrid, Spain.. mlbotet@hup.es
SO HUMAN IMMUNOLOGY, (2000 Jan) 61 (1) 7-17. Ref: 108
Journal code: G9W; 8010936. ISSN: 0198-8859.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LA English
FS Priority Journals
EM 200003
ED Entered STN: 20000314
Last Updated on STN: 20000314
Entered Medline: 20000302
AB Human natural killer (NK) cells specifically interact with major histocompatibility complex (MHC) class I molecules employing different receptor systems, shared with subsets of alphabeta and gammadelta T lymphocytes. Killer cell immunoglobulin-like receptors (KIRs) recognize groups of human leukocyte antigen (HLA) class Ia proteins displaying common structural features at the alpha-1 domain; among them, KIR2DL4 has been proposed to specifically interact with the class Ib molecule HLA-G1. Members of a related family of immunoglobulin (Ig)-like receptors (ILT2 or LIR-1 and ILT4 or LIR-2), expressed by other leukocyte lineages, interact with a broad spectrum of class Ia molecules and HLA-G1. On the other hand, CD94/NKG2-A(-C) and **NKG2D** lectin-like receptors, respectively, recognize the class Ib molecules HLA-E and MICA. A recurrent finding within the different receptor families is the existence of pairs of homologous molecules that often share the same ligands but display divergent functions. Inhibitory receptors tend to exhibit an affinity for HLA molecules higher than their activating counterparts. Recruitment of SH2 domain-bearing tyrosine phosphatases (SHP) by cytoplasmic phosphorylated immunoreceptor tyrosine-based inhibition motifs (ITIMs) is a crucial event for the inhibitory signalling pathway. By contrast, triggering receptors assemble with homodimers of immune tyrosine-based activation motif (ITAM)-bearing adaptor molecules (i.e., DAP12, CD3 xi) that engage tyrosine kinases (ZAP70 and syk).
CT Check Tags: Human
Histocompatibility Antigens Class I: IM, immunology
*Histocompatibility Antigens Class I: ME, metabolism
*Killer Cells, Natural: IM, immunology
Leukocytes: IM, immunology
Ligands
Receptors, Immunologic: CL, classification
Receptors, Immunologic: GE, genetics
Receptors, Immunologic: IM, immunology
***Receptors, Immunologic: ME, metabolism**

L5 ANSWER 10 OF 11 MEDLINE
AN 1999357865 MEDLINE
DN 99357865 PubMed ID: 10426994
TI An activating immunoreceptor complex formed by **NKG2D** and DAP10.
CM Comment in: Science. 1999 Jul 30;285(5428):645-6
AU Wu J; Song Y; Bakker A B; Bauer S; Spies T; Lanier L L; Phillips J H
CS DNAX Research Institute, 901 California Avenue, Palo Alto, CA 94304, USA.
NC AI30581 (NIAID)
SO SCIENCE, (1999 Jul 30) 285 (5428) 730-2.
Journal code: UJ7; 0404511. ISSN: 0036-8075.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-AF072844; GENBANK-AF072845; GENBANK-AF072846; GENBANK-AF122904; GENBANK-AF122905
EM 199908
ED Entered STN: 19990827
Last Updated on STN: 19990827
Entered Medline: 19990816
AB Many immune receptors are composed of separate ligand-binding and signal-transducing subunits. In natural killer (NK) and T cells, DAP10 was identified as a cell surface adaptor protein in an activating receptor complex with **NKG2D**, a receptor for the stress-inducible and

tumor-associated major histocompatibility complex molecule MICA. Within the DAP10 cytoplasmic domain, an Src homology 2 (SH2) domain-binding site was capable of recruiting the p85 subunit of the phosphatidylinositol 3-kinase (PI 3-kinase), providing for **NKG2D**-dependent signal transduction. Thus, **NKG2D**-DAP10 receptor complexes may activate NK and T cell responses against MICA-bearing tumors.

CT Check Tags: Animal; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
1-Phosphatidylinositol 3-Kinase: ME, metabolism
Amino Acid Sequence
Binding Sites
Cell Line
Cytotoxicity, Immunologic
*Killer Cells, Natural: IM, immunology
Killer Cells, Natural: ME, metabolism
Ligands
*Lymphocyte Transformation
Membrane Proteins: CH, chemistry
Membrane Proteins: GE, genetics
*Membrane Proteins: ME, metabolism
Mice
Molecular Sequence Data
Neoplasms: IM, immunology
Phosphorylation
Phosphotyrosine: ME, metabolism
Receptors, Immunologic: CH, chemistry
Receptors, Immunologic: GE, genetics
***Receptors, Immunologic: ME, metabolism**
Signal Transduction
*T-Lymphocytes: IM, immunology
T-Lymphocytes: ME, metabolism
Tumor Cells, Cultured
src Homology Domains

L5 ANSWER 11 OF 11 MEDLINE
AN 1999357864 MEDLINE
DN 99357864 PubMed ID: 10426993
TI Activation of NK cells and T cells by **NKG2D**, a receptor for stress-inducible MICA.
CM Comment in: Science. 1999 Jul 30;285(5428):645-6
AU Bauer S; Groh V; Wu J; Steinle A; Phillips J H; Lanier L L; Spies T
CS Fred Hutchinson Cancer Research Center, Clinical Research Division, 1100 Fairview Avenue North, Seattle, WA 98109, USA.
NC PO1 CA18221 (NCI)
RO1 AI30581 (NIAID)
SO SCIENCE, (1999 Jul 30) 285 (5428) 727-9.
Journal code: UJ7; 0404511. ISSN: 0036-8075.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199908
ED Entered STN: 19990827
Last Updated on STN: 19990827
Entered Medline: 19990816
AB Stress-inducible MICA, a distant homolog of major histocompatibility complex (MHC) class I, functions as an antigen for gammadelta T cells and is frequently expressed in epithelial tumors. A receptor for MICA was detected on most gammadelta T cells, CD8+ alphabeta T cells, and natural killer (NK) cells and was identified as **NKG2D**. Effector cells from all these subsets could be stimulated by ligation of **NKG2D**. Engagement of **NKG2D** activated cytolytic responses of gammadelta T cells and NK cells against transfectants and epithelial tumor cells

expressing MICA. These results define an activating immunoreceptor-MHC ligand interaction that may promote antitumor NK and T cell responses.

CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Cytotoxicity, Immunologic
*Histocompatibility Antigens Class I: IM, immunology
Histocompatibility Antigens Class I: ME, metabolism
Jurkat Cells
*Killer Cells, Natural: IM, immunology
Ligands
Lymphocyte Subsets: IM, immunology
*Lymphocyte Transformation
Membrane Proteins: ME, metabolism
Receptors, Antigen, T-Cell, gamma-delta: IM, immunology
Receptors, Immunologic: CH, chemistry
Receptors, Immunologic: GE, genetics
***Receptors, Immunologic: IM, immunology**
Receptors, Immunologic: ME, metabolism
Signal Transduction
*T-Lymphocytes: IM, immunology
Transfection
Tumor Cells, Cultured

L8 ANSWER 1 OF 7 MEDLINE
AN 2001563617 IN-PROCESS
DN 21521655 PubMed ID: 11567108
TI Immunology: stress, nk receptors, and immune surveillance.
AU Pardoll D M
SO SCIENCE, (2001 Oct 19) 294 (5542) 534-6.
Journal code: UJ7; 0404511. ISSN: 0036-8075.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20011022
Last Updated on STN: 20011022
AB It has long been suspected that natural killer (NK) cells are involved in immune surveillance. Now comes new work, described by Pardoll in his Perspective, showing that gd T cells expressing an NK cell receptor called **NKG2d** are important for detecting precancerous skin epithelial cells in mice (Girardi et al.). Engagement of **NKG2d** with its ligands Rae-1 or H60 expressed on mouse epidermal cells treated with carcinogens results in activation of gd T cells, which eliminate the precancerous epidermal cells before they become established as **tumors**.

L8 ANSWER 2 OF 7 MEDLINE
AN 2001525841 IN-PROCESS
DN 21457265 PubMed ID: 11562472
TI Ectopic expression of retinoic acid early inducible-1 gene (RAE-1) permits natural killer cell-mediated rejection of a MHC class I-bearing **tumor** in vivo.
AU Cerwenka A; Baron J L; Lanier L L
CS Department of Microbiology and Immunology and the Cancer Research Institute, University of California, San Francisco, CA 94143-0414.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2001 Sep 25) 98 (20) 11521-6.
Journal code: PV3; 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English

FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20010927
Last Updated on STN: 20010927
AB In 1986, Karre and colleagues reported that natural killer (NK) cells rejected an MHC class I-deficient **tumor** cell line (RMA-S) but they did not reject the same cell line if it expressed MHC class I (RMA). Based on this observation, they proposed the concept that NK cells provide immune surveillance for "missing self," e.g., they eliminate cells that have lost class I MHC antigens. This seminal observation predicted the existence of inhibitory NK cell receptors for MHC class I. Here, we present evidence that NK cells are able to reject **tumors** expressing MHC class I if the **tumor** expresses a ligand for **NKG2D**. Mock-transfected RMA cells resulted in **tumor** formation. In contrast, when RMA cells were transfected with the retinoic acid early inducible gene-1 gamma or delta (RAE-1), ligands for the activating receptor **NKG2D**, the **tumors** were rejected. The **tumor** rejection was mediated by NK cells, and not by CD1-restricted NK1.1(+) T cells. No T cell-mediated immunological memory against the parental **tumor** was generated in the animals that had rejected the RAE-1 transfected **tumors**, which succumbed to rechallenge with the parental RMA **tumor**. Therefore, NK cells are able to reject a **tumor** expressing RAE-1 molecules, despite expression of self MHC class I on the **tumor**, demonstrating the potential for NK cells to participate in immunity against class I-bearing malignancies.

L8 ANSWER 3 OF 7 MEDLINE
AN 2001468526 IN-PROCESS
DN 21404051 PubMed ID: 11513139
TI The UL16-binding proteins, a novel family of MHC class I-related ligands for **NKG2D**, activate natural killer cell functions.
AU Sutherland C L; Chalupny N J; Cosman D
CS Department of Molecular Biology, Immunex Corporation, Seattle, Washington 98101, USA.. sutherlandc@immunex.com
SO IMMUNOLOGICAL REVIEWS, (2001 Jun) 181 185-92.
Journal code: GG4; 7702118. ISSN: 0105-2896.
CY Denmark
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20010830
Last Updated on STN: 20010830
AB The UL16-binding proteins (ULBPs) are a novel family of MHC class I-related molecules (MICs) that were identified based on their ability to bind to the human cytomegalovirus (HCMV) glycoprotein UL16. UL16 also binds to a member of another family of MHC class I-like molecules, MICB. The ULBPs and MICs are ligands for **NKG2D**/DAP10, an activating receptor expressed by natural killer (NK) cells and other immune effector cells, and this interaction can be blocked by UL16. Engagement of **NKG2D**/DAP10 by ULBPs or MICs expressed on a target cell can overcome an inhibitory signal generated by NK-cell recognition of MHC class I molecules and trigger NK cytotoxicity. ULBPs elicit their effects on NK cells by activating the janus kinase 2, signal transducer and activator of transcription 5, extracellular-signal-regulated kinase mitogen-activated protein kinase and Akt/protein kinase B signal transduction pathways. Although ULBPs alone activate multiple signaling pathways and induce modest cytokine production, ULBPs synergize strongly with interleukin-12 for production of interferon-gamma by NK cells. This finding is consistent with reports in T cells that **NKG2D**/DAP10 can act as a co-stimulatory receptor in a similar manner as CD28. The possible roles of ULBPs in mediating immune responses to viruses and **tumors** and the potential mechanisms by which UL16 may allow HCMV to evade immune detection are areas of active investigation.

L8 ANSWER 4 OF 7 MEDLINE
AN 2001434402 MEDLINE
DN 21139817 PubMed ID: 11244035
TI Activating receptors and coreceptors involved in human natural killer cell-mediated cytolysis.
AU Moretta A; Bottino C; Vitale M; Pende D; Cantoni C; Mingari M C; Biassoni R; Moretta L
CS Dipartimento di Medicina Sperimentale, Universita degli Studi di Genova, Italy.. alemoret@unige.it
SO ANNUAL REVIEW OF IMMUNOLOGY, (2001) 19 197-223. Ref: 127
Journal code: ALO; 8309206. ISSN: 0732-0582.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 200108
ED Entered STN: 20010806
Last Updated on STN: 20010806
Entered Medline: 20010802
AB Natural killer cells can discriminate between normal cells and cells that do not express adequate amounts of major histocompatibility complex (MHC) class I molecules. The discovery, both in mouse and in human, of MHC-specific inhibitory receptors clarified the molecular basis of this important NK cell function. However, the triggering receptors responsible for positive NK cell stimulation remained elusive until recently. Some of these receptors have now been identified in humans, thus shedding some light on the molecular mechanisms involved in NK cell activation during the process of natural cytotoxicity. Three novel, NK-specific, triggering surface molecules (NKp46, NKp30, and NKp44) have been identified. They represent the first members of a novel emerging group of receptors collectively termed natural cytotoxicity receptors (NCR). Monoclonal antibodies (mAbs) to NCR block to differing extents the NK-mediated lysis of various **tumors**. Moreover, lysis of certain **tumors** can be virtually abrogated by the simultaneous masking of the three NCRs. There is a coordinated surface expression of the three NCRs, their surface density varying in different individuals and also in the NK cells isolated from a given individual. A direct correlation exists between the surface density of NCR and the ability of NK cells to kill various **tumors** . NKp46 is the only NCR involved in human NK-mediated killing of murine target cells. Accordingly, a homologue of NKp46 has been detected in mouse. Molecular cloning of NCR revealed novel members of the Ig superfamily displaying a low degree of similarity to each other and to known human molecules. NCRs are coupled to different signal transducing adaptor proteins, including CD3 zeta, Fc epsilon RI gamma, and KARAP/DAP12. Another triggering NK receptor is **NKG2D**. It appears to play either a complementary or a synergistic role with NCRs. Thus, the triggering of NK cells in the process of **tumor** cell lysis may often depend on the concerted action of NCR and **NKG2D**. In some instances, however, it may uniquely depend upon the activity of NCR or **NKG2D** only. Strict **NKG2D**-dependency can be appreciated using clones that, in spite of their NCR(dull) phenotype, efficiently lyse certain epithelial **tumors** or leukemic cell lines. Other triggering surface molecules including 2B4 and the novel NKp80 appear to function as coreceptors rather than as true receptors. Indeed, they can induce natural cytotoxicity only when co-engaged with a triggering receptor. While an altered expression or function of NCR or **NKG2D** is being explored as a possible cause of immunological disorders, 2B4 dysfunction has already been associated with a severe form of immunodeficiency. Indeed, in patients with the X-linked lymphoproliferative disease, the inability to control Epstein-Barr virus

infections may be consequent to a major dysfunction of 2B4 that exerts inhibitory instead of activating functions.

CT Check Tags: Animal; Human; Support, Non-U.S. Gov't
Antibodies, Monoclonal: IM, immunology
Antibodies, Monoclonal: PD, pharmacology
Carrier Proteins: IM, immunology
Cloning, Molecular
*Cytotoxicity, Immunologic: IM, immunology
Epstein-Barr Virus Infections: IM, immunology
Histocompatibility Antigens Class I: IM, immunology
*Killer Cells, Natural: IM, immunology
Lymphoproliferative Disorders: IM, immunology
Membrane Glycoproteins: CH, chemistry
Membrane Glycoproteins: IM, immunology
Mice
Multigene Family
Neoplasms: IM, immunology
Neoplasms, Experimental: IM, immunology
Receptors, Immunologic: AI, antagonists & inhibitors
Receptors, Immunologic: CH, chemistry
*Receptors, Immunologic: IM, immunology
Signal Transduction

L8 ANSWER 5 OF 7 MEDLINE
AN 2001106858 MEDLINE
DN 20578924 PubMed ID: 11137207
TI Triggering receptors involved in natural killer cell-mediated cytotoxicity against choriocarcinoma cell lines.
AU Sivori S; Parolini S; Marcenaro E; Millo R; Bottino C; Moretta A
CS Dipartimento di Medicina Sperimentale, Universita di Genova, Genova, Italy.
SO HUMAN IMMUNOLOGY, (2000 Nov) 61 (11) 1055-8.
Journal code: G9W. ISSN: 0198-8859.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200102
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010208
AB The lack of classical HLA-class I molecules on trophoblast is necessary to prevent allorecognition by maternal CTL, but may induce activation of NK cells. A protective role against NK cells equipped of suitable inhibitory receptors has been proposed for nonclassical HLA-class I molecules including HLA-E and HLA-G. In the present study we show that the NK-mediated killing of two choriocarcinoma cell lines, JAR and JEG3, is induced upon engagement of natural cytotoxicity receptors (NCR) with their specific ligands. In particular, we show that NKp44, a triggering receptor expressed at the NK cell surface only after in vitro culture in the presence of IL-2, plays a central role in triggering NK cytotoxicity against trophoblast cells. Also NKp46 appear to contribute to this function by cooperating with NKp44. On the other hand, other triggering receptors such as NKp30, 2B4, and **NKG2D** are not involved in killing of choriocarcinoma. Our findings suggest that resistance of trophoblast to NK-mediated cytotoxicity is the result of insufficient activating interactions between the various triggering NK receptors and their target cell ligands. On the other hand, the interaction of nonclassical HLA class I molecules with inhibitory NK receptors appears to play only a marginal role in regulating the susceptibility of choriocarcinoma to NK mediated cytotoxicity.
CT Check Tags: Human; Support, Non-U.S. Gov't
Antibodies, Monoclonal: IM, immunology

*Choriocarcinoma: IM, immunology
Cytotoxicity Tests, Immunologic
*Cytotoxicity, Immunologic
Histocompatibility Antigens Class I: IM, immunology
Interleukin-2: PD, pharmacology
Killer Cells, Natural: DE, drug effects
*Killer Cells, Natural: IM, immunology
*Receptors, Immunologic: IM, immunology
Tumor Cells, Cultured

L8 ANSWER 6 OF 7 MEDLINE
AN 2000045048 MEDLINE
DN 20045048 PubMed ID: 10574749
TI Natural killer cells: stress out, turn on, tune in.
AU Diefenbach A; Raulet D H
CS Department of Molecular and Cell Biology, Cancer Research Laboratory, 485 Life Sciences Addition, University of California at Berkeley, Berkeley, 94720-3200, USA.
SO CURRENT BIOLOGY, (1999 Nov 18) 9 (22) R851-3. Ref: 14
Journal code: B44; 9107782. ISSN: 0960-9822.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200005
ED Entered STN: 20000518
Last Updated on STN: 20000518
Entered Medline: 20000511
AB Natural killer cells attack **tumor** cells, infected cells and some normal cells, but the basis of their specificity is not completely understood. Recent studies indicate that epithelial **tumor** cells upregulate a stress-induced MHC class-I-like protein termed MICA, triggering NK cells via a recently described receptor called **NKG2D**.
CT Check Tags: Animal; Human
*Carcinoma: IM, immunology
*Heat-Shock Proteins: IM, immunology
*Histocompatibility Antigens Class I: IM, immunology
*Killer Cells, Natural: IM, immunology
Lymphocyte Transformation
Membrane Proteins: CH, chemistry
*Membrane Proteins: IM, immunology
Mice
*Models, Immunological
*Neoplasm Proteins: IM, immunology
Receptors, Immunologic: CH, chemistry
*Receptors, Immunologic: IM, immunology
T-Lymphocytes: IM, immunology

L8 ANSWER 7 OF 7 MEDLINE
AN 96235029 MEDLINE
DN 96235029 PubMed ID: 8642329
TI An autosomal dominant locus, Nka, mapping to the Ly-49 region of a rat natural killer (NK) gene complex, controls NK cell lysis of allogeneic lymphocytes.
AU Dissen E; Ryan J C; Seaman W E; Fossum S
CS Department of Anatomy, University of Oslo, Norway.
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1996 May 1) 183 (5) 2197-207.
Journal code: I2V; 2985109R. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS Priority Journals
OS GENBANK-U56822; GENBANK-U56823; GENBANK-U56824; GENBANK-U56863
EM 199607
ED Entered STN: 19960726
Last Updated on STN: 19980206
Entered Medline: 19960718

AB Natural Killer (NK) cells can recognize and kill MHC-incompatible normal bone marrow-derived cells. Presently characterized MHC-binding receptors on NK cells, including the Ly-49 family in the mouse, transmit inhibitory signals upon binding to cognate class I MHC ligands. Here we study in vivo NK-mediated lysis of normal allogeneic lymphocytes in crosses between alloreactivity-competent PVG rats and alloreactivity-deficient DA rats. NK cells from both strains are able to lyse standard **tumor** targets. We identify an autosomal dominant locus, Nka, that controls NK-mediated alloreactivity. Individuals carrying the dominant PVG allele in single dose were fully competent in eliminating allogeneic target cells, suggesting that Nka encodes or regulates a gene product inducing or activating alloreactivity. By linkage analysis and pulsed field gel electrophoresis, a natural killer gene complex (NKC) on rat chromosome 4 is described that contains the rat NKR-P1 and Ly-49 multigene families plus a rat **NKG2D** homologue. Nka maps within the NKC, together with the most telomeric Ly-49 family members, but separate from **NKG2D** and the NKR-P1 family. The Nka-encoded response, moreover, correlates with the expression of transcripts for Ly-49 receptors in NK cell populations, as Northern blot analysis demonstrated low expression of Ly-49 genes in DA NK cells, in contrast to high expression in alloreactivity-competent PVG, (DA X PVG)F1, and PVG.1AVI NK cells. The low Ly-49 expression in DA is not induced by MHC haplotype, as demonstrated by high expression of Ly-49 in the DA MHC-congenic PVG.1AVI strain. Finally, we have cloned and characterized the first four members of the rat Ly-49 gene family. Their cytoplasmic domains demonstrate substantial heterogeneity, consistent with the hypothesis that different Ly-49 family members may subserve different signaling functions.

CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
Amino Acid Sequence
Antigens, Surface: IM, immunology
Base Sequence
*Chromosome Mapping
Consensus Sequence
Crosses, Genetic
DNA Primers
Exons
*Genes, Dominant
Histocompatibility Antigens Class I: IM, immunology
Isoantigens: IM, immunology
*Killer Cells, Natural: IM, immunology
Major Histocompatibility Complex
Membrane Glycoproteins: BI, biosynthesis
*Membrane Glycoproteins: GE, genetics
Mice
Molecular Sequence Data
Phylogeny
Polymerase Chain Reaction
Pseudogenes
Rats
Rats, Inbred F344
Rats, Inbred Lew
Rats, Inbred Strains
Sequence Homology, Amino Acid